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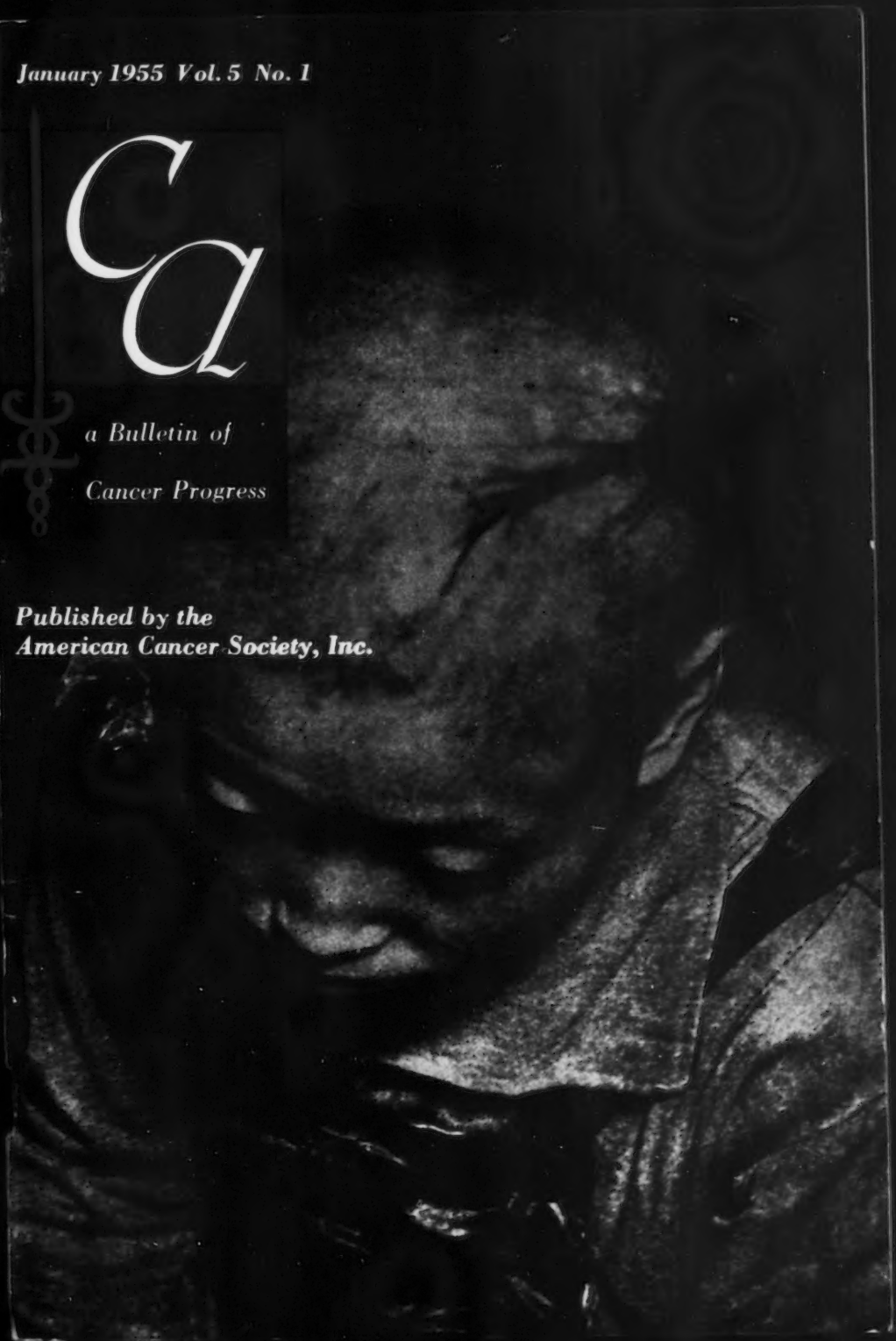

more good than evil

A half century ago Pierre Curie said, that "in criminal hands, radium might become dangerous . . . is humanity ripe enough to profit by learning the secrets of nature, or might not that knowledge prove harmful? I believe that humanity will obtain *more good than evil* from future discoveries."

The discovery of radioactivity by Becquerel and the Curies has been an incalculable blessing, and radium has eased pain, parried death, and given life to numberless cancer sufferers. And yet Pierre Curie was a greater prophet than he knew, for this same discovery was the seed from which was developed the most potent agent for suffering, death, and mass destruction the world has ever known. Radioactivity, the bane and the blessing of modern man, is an example of the utter impartiality of science in ministering to the best and the worst that is in us. Science is not to blame, for it is the servant of man. The fault lies in man himself, who wills to put science to such paradoxical uses.

On the credit side of the ledger of man's stewardship of radioactivity is the application of the many forms of radiation to the treatment of cancer—first Roentgen's "new kind of rays," then radium and radon with the numerous refinements and techniques, followed by the radioactive isotopes resulting from nuclear fission. Advances in supervoltage therapy, particle-accelerating beams, precision targeting, rotation therapy, and induction of greater tumor susceptibility to radiation have made radiotherapy a worthy partner to surgery—previously the sole cure for cancer.

Of greatest importance in the long-term control of cancer are the rapidly accumulating data concerning the effects of ionizing radiations on normal and cancer cells, particularly the effects on genes and chromosomes and the effects in nucleic acid synthesis.

Thus radiant energy from the many sources now available has become a valuable factor not only in the immediate therapy of cancer but also in research by revealing more and more of the intimate physiology of the cell in which the cause of cancer still lies hidden.

Surely from the discoveries of Roentgen, of the Curies, and of those following them has come MORE GOOD THAN EVIL.

George E. Pfahler

Cover—

This little girl was a victim of the atomic bomb explosion at Nagasaki on August 9, 1945. More impressive, perhaps, than her alopecia is her deeply wistful expression—symbolic of the bewilderment of all mankind now caught between the forces of discovery and destruction.

NEWSLETTER

JANUARY, 1955

Protection against the Atom: The basic work of several scientists may have given us a preview of the awesome radiation effects on humans of bursting atomic bombs. A split second of exposure may set in motion a tragic chain of biological events that cover many decades or generations of human life. Furth (Children's Hosp., Boston) has observed in mice exposed to atomic-bomb blasts in the Pacific the immediate and the delayed effects of atomic-bomb radiation. The effects, like the energy, vary enormously, according to the power of the bomb and the distance from the blast epicenter. Because there has been a distinct parallel between the mouse pathology and that so far observed in victims of the Nagasaki and Hiroshima bombings, there is some justification for expecting additional human damage to come to light in Japan many years from now. In the order of their appearance, the cast of characters in the radiation-effects drama runs something like this: cataracts, infection, hair graying, albinism, leukemia, pituitary and other tumors, nephrosclerosis, and renal failures. Some of the investigators, including Furth, feel that it is almost as though powerful premature aging influences were released with the bomb burst--hair graying, cataracts, anomalies of the iris, and vascular changes in the kidney resembling arteriosclerosis. The incidence of leukemia is increased many times. In those situated at the correct radius from the center of the burst, leukemia cases may be multiplied a hundred or more times normal. The pituitary tumors fill one third of the cranial space, and, oddly enough, they are potent producers of ACTH. This may be a feed-back phenomenon occasioned by the destruction of the adrenal cortex --the futile effort of the pituitary to stimulate a destroyed or damaged and nonfunctional adrenal. Animals become susceptible to infections and obese and show some characteristics of Cushing's syndrome. On the bright side of the ledger is the hope that fundamental observations made by Gardner (Yale U.) and others may supply a key to survival. From such studies have come an understanding of the endocrine imbalances involved and ways of correcting them, if they can be anticipated or detected early enough. Such

things as these have been found: Total-body radiation depresses gonadal function and stimulates pituitary function. (Would administration of cortical hormones and/or gonadal hormones control this situation?) If the thyroid is destroyed or thyroxin becomes deficient (as with administration of radioactive iodine), the resultant imbalance and pituitary tumors can be controlled with doses of thyroid hormone. Testosterone prevents leukemia in some mouse strains. Such observations as these--and others involving common tumors of the ovary, breast, and uterus--have given science a working hypothesis on which to build civilian defenses for the atomic age.

Radiomimetic Compounds: Compounds like nitrogen mustard and triethylenemelamine (TEM) may reproduce some of the effects of roentgen rays but not others. This was brought out in a report by Nadkarni, Goldenthal, and Smith (George Washington U.) on the ability of certain drugs to offset radiation effects. The investigators pointed out that cysteine, beta-mercaptoethylamine, sodium nitrite, and other substances, when applied prior to roentgen rays, can offset the toxic effects of the radiation. Fortified by these substances, mice may undergo a lethal (700 r) dose of roentgen rays or similar dose of nitrogen mustard with complete protection. The drugs gave no protection against TEM, however. The group found that cystamine afforded better protection than cysteine against roentgen rays.

NOTES FROM THE AMERICAN CANCER SOCIETY ANNUAL MEETING

Scientific sessions were concerned with, as Popma (Society president) termed it, "the brightest phase" of the current cancer control picture -- uterine cancer. Thanks to early detection and the decided drop (substantially more than 10 per cent) in cervical-cancer-mortality rates, general cancer death rates among women have leveled off and begun to decline.

Other sessions were concerned largely with lung cancer -- the dark and dismal disease against which little progress has been made. Lung-cancer-death rates among men are doubling with each passing decade. Early detection remains a problem of prime magnitude.

Cervical Cancer: Reports on etiology and demography indicated that exogenous agents play a leading role in this condition. Heredity is of little or no consequence.

(Continued after page 36)

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Keeping up

Gastric Ulcer Differentiated from Gastric Cancer

One hundred thirty-eight patients with gastric ulcer were studied in an effort to determine the best criteria for early surgical operation. This represents 151 hospital admissions and includes 162 separate ulcers. Nine patients with ulcerative lesions caused by or associated with obvious cancer and so reported on the initial roentgen-ray examination were excluded from this study. There were three patients with proved and one with presumed cancer in the entire group, which included 60 patients treated medically by choice and 42 patients in whom early operation was performed or was considered desirable for assurance against cancer. The patient's age and the location of the ulcer are of some diagnostic importance, whereas the duration and pattern of symptoms, the amount of weight loss, the degree of acidity of the fasting specimen, and the size of the ulcer are not of appreciable significance in differentiating benign from malignant lesions. Rapid and complete healing, although not infallible, is considered acceptable proof that an ulcer is benign. Prompt surgery as assurance against cancer is advised if the roentgen-ray findings are at all suggestive of cancer, if there is histamine achlorhydria, or if the ulcer is located on the greater curvature. With these exceptions the authors believe that patients less than 50 years of age should receive a trial on medical management. For older patients in whom age is the only factor suggesting a high probability of cancer, the decision for or against early operation is determined by the estimation of surgical risk. Surgical treatment is also recommended if the ulcer fails to heal under medical therapy or if it recurs. There is need for greater uniformity in the methods of studying these cases and for a continuing re-evaluation of the diagnostic significance of various clinical and roentgen-ray findings.

Gott, J. R., Jr.; Shapiro, D., and Kelty, K. C.: Gastric ulcer; a study of 138 patients. New England J. Med. 250:499-504, Mar. 25, 1954.

Cancer of the Larynx and Laryngopharynx

Clinical investigation over a period of twenty years reveals that the five- and ten-year results are practically equivalent to surgical results for comparable cases. In limited lesions without fixation or obstruction, high cure rates are obtained. Laryngeal cancer is a geriatric problem because three fifths of all cases occur in the 50- to 69-year age group and patients more than 70 years of age comprise another 20 per cent. Nine times as many men are afflicted as women. Of the 220 cases treated, all were squamous epithelial-cell carcinomas except for two adenocarcinomas. Classification is based on anatomy and surgical indications. Lesions involving both intrinsic and extrinsic larynx are classified according to laryngopharyngeal involvement. After diagnosis is established by biopsy, roentgenographic studies, and laminagraphy, a six- or seven-week course of treatment is instituted. The patient, either lying down or sitting up, is exposed to 150 r daily of 200 to 400 kv. radiation from 60 cm. through a field depending in size upon the extent and location of the

...with Cancer

tumor. If the airway is narrow, treatment may be administered slowly in small doses, together with antibiotics, to prevent swelling and inflammation. Usually the disease disappears at the end of treatment, although one month should be allowed for complete subsidence of the roentgen-ray reaction. Lesions located in the larynx proper or the anterior laryngopharynx respond best to therapy. Chance of cure is reduced one half if there is fixation and further reduced by laryngeal obstruction requiring tracheostomy before or during radiation therapy.

Harris, W.; Silverstone, S. M., and Kramer, R.: Roentgen therapy for cancer of the larynx and laryngopharynx; twenty years' experience. Am. J. Roentgenol. 71:813-825, May, 1954.

Effect of Age on Clinical Course of Cancer

According to the author, there is a widespread impression that the clinical course of cancer in young patients is more rapid than in old patients. Clinicians were asked for data that might indicate that the clinical behavior of a specific form of cancer varied with the age of the patient. All replies relative to cancer of the rectum were identical; no clinician had specific information, but each confirmed the general impression that there is a poorer prognosis in younger persons, which is attributed to a delay in diagnosis. For cancer of the stomach and prostate, a poor prognosis was noted in the younger group again attributed to delay in diagnosis owing to a lowered index of suspicion. In the case of seminoma of the testicle the older age group showed the poorer prognosis; this was again attributed to delay in diagnosis because of failure to consider a slight enlargement of the testicle as abnormal in an elderly man. Data obtained for melanoma, breast cancer, and acute leukemia did suggest a degree of correlation with the age of the patient, but a study of their behavior in hosts of various ages might be expected to show differences as a reflection of the influence of those aspects of endocrine metabolism that vary with age, that is, the sex glands. In women with breast cancer, age as well as hormone therapy exert a definite influence. If women are fifteen or more years beyond the menopause, administration of stilbestrol and female hormones produces regresssion in the size of most breast cancers and encourages the healing process of most cancerous ulcerations. In women who have not reached the menopause, the administration of estrogens appears to accelerate the rate of growth of the cancer. Adenocarcinoma of the female breast, therefore, has a biological behavior that varies according to the age of the patient. After commenting on the rapid growth of breast cancer during pregnancy, the author shows that the clinical behavior of melanoma has some similarity to that of breast cancer. Leukemia also shows a relationship to age. There is an early peak in the incidence of this disease occurring in those less than 5 years of age, and a much higher peak is reached at approximately 80 years of age. Acute leukemia is predominant in early childhood; the chronic stage increases in frequency with advancing age. It might be supposed that either we are dealing with two different diseases or that age modifies the character of this disease. The author

deduces from these observations, that, inasmuch as the same histological and anatomical types of cancer can behave differently in different age groups, clinical trials of therapeutic agents must always include not only a spectrum of tumors but of hosts as well.

Klopp, C. T.: Some remarks on the effect of age in the clinical course of cancer. J. Am. Women's A. 9:109-112, April, 1954.

Survival Rates Following Radical Mastectomy

A study of fifteen- to forty-year survival rates following radical mastectomy performed on women for carcinoma of the breast compiled at the Mayo Clinic is presented. The cases presented comprise, for the calculation of the fifteen-year–survival rates, 4637 patients with unilateral carcinoma of the breast on whom radical mastectomy was performed in 1934 or earlier, of whom 4563 (98.4 per cent) were traced. The author was interested in determining certain factors that influence the prognosis as shown by the survival rates following operation. Following radical mastectomy prognosis appears related to many different factors, some of the more important of which are: the extent of involvement at the time of operation; the degree of malignancy as shown by microscopic examination of the primary lesion; the presence of other associated conditions, such as pregnancy and lactation; the general constitutional diseases, such as diabetes; and the age of the patient. There is no known method of determining what the prognosis will be in any individual case. Many patients have obtained the opinion that they are "cured" of malignant disease if, on examination five years after operation, no evidence of the malignant disease is found. A study of long-term–survival rates shows that local recurrence or metastatic lesions may occur fifteen or more years after the operation. Of the 4563 traced patients, 2918 (63.9 per cent) were found to have had axillary node metastasis at the time of operation. Of these, 351 (12.0 per cent) lived fifteen or more years, and of the 1645 without axillary node metastasis, 793 (48.2 per cent) lived fifteen or more years. The author concludes that studies on long-term–survival rates following radical mastectomy for carcinoma of the breast show that it is impossible to determine definitely the prognosis in an individual case either before or at the time of the operation, and that patients with unilateral high-grade malignant growths with metastasis as well as patients who subsequently develop a malignant growth in the remaining breast with metastasis may survive many years following operation.

Harrington, S. W.: Fifteen-year to forty-year survival rates following radical mastectomy for cancer of the breast. Ann. Surg. 137:843-849, June, 1953.

Polycythemia Vera in Relation to Myeloid Metaplasia and Leukemia

Polycythemia vera or erythremia is a chronic progressive disease characterized by an initial increase in the number of erythrocytes, which may be accompanied by a leukocytosis, thrombocytosis, splenomegaly, and ruddy cyanosis. The concept of a total panmyelosis with expansion of the active red marrow to encompass the total potential marrow space received increasing support from biopsy and postmortem examination of the marrow in early erythremia; the frequent association of leukemia and leukemic blood pictures, the occurrence of immature red and white blood cells in the peripheral blood, and the thrombocytosis lend support to the hypothesis that erythremia is a chronic generalized bone-marrow disease. As cases of polycythemia vera were followed over a prolonged period of time, it was noted that the erythrocytosis was merely an initial facet of a complex disease process that frequently terminated in leukemia, osteosclerosis, myelofibrosis, myeloid metaplasia, and other diverse pathological entities. The concept of the neoplastic nature of erythremia thus arose and the disease now is becoming recognized as being similar in origin to other myeloproliferative syndromes. The relatively prolonged course of the disease and the apparent lack of invasiveness manifested by the proliferating cells have been

cited as evidence against the neoplastic nature of erythremia; however, well-differentiated malignant cells are functionally close to normal cells and may have a benign course for many years. Leukemia and myelofibrosis with myeloid metaplasia should not truly be classified as a complication but rather as stages of erythremia occurring incident to the natural course and duration of the disease. Of 144 deaths (sum of three separate series including author's) in polycythemia vera treated with roentgen rays or P^{32}, about 25 per cent were due to leukemia and myelofibrosis. As far as chronicity is concerned, Tinney and his associates reported the high incidence of leukemia, as much as 80 per cent, occurring in patients surviving more than fifteen years and emphasized the direct relation between duration of the erythremic state and abnormal white-cell proliferation. Reduction in the blood volume, suppression of the increased marrow activity, and reduction in the white cells and the platelets are all essential to the successful treatment of polycythemia vera. Elective surgical intervention should be avoided (because of the paradoxical problem of coagulation and hemmorrhage with normal or elevated blood platelets) unless normal blood values have been achieved. Initial rapid reduction of the blood volume followed by the use of P^{32} has given the most satisfactory results. Marrow-suppressive therapy requires caution and must be individualized particularly when triethylenemelamine is used. P^{32} remains the treatment of choice.

Wasserman, L. R.: Polycythemia vera—its course and treatment: relation to myeloid metaplasia and leukemia. Bull. New York Acad. Med. 30:343-375, May, 1954.

Age and Prognosis in Thyroid Cancer

Surgeons who do not have access to frozen-section diagnosis can evaluate thyroid cancer quite accurately by the patient's age. If the patient is less than 40 years, the tumor nearly always has a very low-grade malignancy, but the prognosis for elderly patients is poor. Thyroid cancer can be divided into two major types, papillary and nonpapillary. In younger persons, growth follows the first pattern and is almost uniformly curable by adequate but not mutilating resection. The primary tumor in the gland should be taken out completely, with cervical and upper mediastinal metastases. Even if neoplastic tissue is predominantly adenomatous or alveolar, most thyroid cancers developing before middle age behave like papillary forms. The rare nonpapillary type noted in those less than 40 is usually angioinvasive adenoma with low-grade malignancy. Carcinoma in the older-age group is generally nonpapillary and dangerous. When areas of anaplasia develop, the prognosis is poor.

Crile, G., Jr., and Hazard, J. B.: Relationship of the age of the patient to the natural history and prognosis of carcinoma of the thyroid. Ann. Surg. 138: 33-38, July, 1953.

Bilateral Adrenalectomy for Prostatic Cancer

Three patients with advanced prostatic carcinoma subjected to bilateral adrenalectomy are cited to support the thesis that bilateral total adrenalectomy is an effective and acceptable procedure for the treatment of selected cases of metastatic prostatic carcinoma that have failed to respond to, or have escaped from, the effects of other methods of anti-androgenic control. The determination of the serum–acid-phosphatase level and examination of the prostatic lesion were the objective means employed in evaluating the results of adrenalectomy. Although subjective changes were difficult to evaluate, a persistent subjective change of nine months' duration may be an acceptable criterion. The time at which the procedure can be most useful may be determined only through careful evaluation of a large number of cases, performed in different stages of the disease. Improvement in surgical technique and the availability of substitution adrenal therapy justify total adrenalectomy in selected cases of prostatic cancer.

Scardino, P. L.; Prince, C. L., and McGoldrick, T. A.: Bilateral adrenalectomy for prostatic cancer. J. Urol. 70:100-109, July, 1953.

at a glance . . .

one-minute abstracts of the current literature on cancer . . .

Au^{198} for Prostatic Cancer

Follow-up studies of a preliminary report previously published (See CA, 4:41, Mar., 1954) on the treatment of 130 patients with carcinoma of the prostate by interstitial radiation with Au^{198} are presented. The basic reasoning underlying the use of this type of radiation therapy is as follows: the small size of even inoperable localized prostatic carcinomas and the fascial configuration around the prostate make such lesions particularly suitable for beta radiation therapy from Au^{198}. A tremendous dose of radioactive energy can be given locally in and about the tumor with little effect more than 3 mm. away. Thus adequate irradiation can be achieved without the high incidence of vesical and rectal damage that is associated with conventional radiation treatment in this area. The most satisfactory dosage has been 2 mc. per gm. of tissue with an upper limit of 150 mc., since, in the higher ranges, the gamma component becomes of increasing importance, and complications occur more frequently. Injection of the radioactive material is done with a pressure syringe equipped with a guard so that deep injection into tissue is impossible. Dissemination of the fluid depends on the pressure with which injections are made. The incidence of complications, particularly of rectal difficulties, has been tremendously decreased with improvements in this technique. The results of treatment of 100 patients observed from three to eighteen months show clinical arrest in forty-eight cases and negative biopsy reports obtained for a significant number. The authors' further studies confirm their earlier experiences and serve to emphasize that tremendous destruction of prostatic cancer, often complete eradication, can be achieved by the injection of Au^{198}.

Flocks, R. H.; Kerr, H. D.; Elkins, H. B., and Culp, D. A.: The treatment of carcinoma of the prostate by interstitial radiation with radioactive gold (Au^{198}): a follow-up report. J. Urol. 71:628-633, May, 1954.

Irradiation Fibromatosis and Fibrosarcoma

Although it is rare for fibrous tissue to become so altered by irradiation as to form a malignant tumor, four cases of fibrosarcoma developing after irradiation therapy are reported here. More frequently irradiation fibromatosis may follow roentgen-ray therapy and such a case is also cited. In all of the four, excessive and poorly conceived roentgen-ray therapy had been given many years previously. Irradiation fibromatosis may blend into fibrosarcoma, which is usually a low-grade lesion and is peculiar in that it kills by local infiltration rather than by distant

metastases. The authors recommend that, when irradiation fibromatosis is first recognized, it should be excised completely, together with all adjacent altered tissues. Such treatment will tend to prevent the development of multiple, focal areas of malignant degeneration. Once the diagnosis of fibrosarcoma has been confirmed, even more extensive procedures may be required with the sacrifice at times of vital structures.

Pettit, V. D.; Chamness, J. T., and Ackerman, L. V.: Fibromatosis and fibrosarcoma following irradiation therapy. Cancer 7:149-158, Jan., 1954.

Detection of Radiation

Values of radioactivity in the human body vary considerably, depending upon the different methods employed in radiation determinations. The emanation method measures only the amount of radium in tissues and therefore gives the lowest values, since nonemanating radioactive substances and short-lived emanations are not detected. Measurements with particle-counting devices or apparatus sensitive to alpha and gamma radiation give the most accurate indication of the internal irradiation burden of the body. The particle-counting and particle-ionizing methods record all the main radioactive elements, including uranium, thorium, and actinium, in addition to detecting the radium element. Radium content of man appears to be within the permissible range of 1×10^{-7} gm. The amounts of radioactive substances deposited in the human body approximate the accepted tolerance values.

Krebs, A. T.: The radioactivity of the human being. Science 119:429-431, April 2, 1954.

Irradiation of the Liver

Favorable results have been reported of treatment of hepatic metastases from carcinoma of the breast, bronchus, or gastrointestinal tract with high-dosage irradiation of the entire liver. The whole liver is irradiated through opposed anterior and posterior fields at 1000 kv. to deliver a tumor dose of 2000 to 3750 r. Some patients receive a single intravenous injection of nitrogen mustard, 0.4 mg. per kg. of body weight, just before the first treatment. Therapy is usually completed in eight days to lessen expense and allow the patient as much time at home as possible. In about two thirds of the cases these results are anticipated: reduction in size of the liver accompanied by a gain in weight and improvement in hepatic function. Profuse night sweating serves as a useful guide, since clearing of this symptom heralds improvement in the patient's general condition. Other symptoms that may be alleviated include pain, anorexia, nausea, vomiting, weakness, fatigue, and abdominal distention. Benefit is very temporary, the relief usually lasting less than two months and the longest reported remission, seven months. Radiation sickness has not been noted nor depression of the bone marrow, even in patients also receiving nitrogen mustard. Edema of the liver has not been a problem. Highest dosages may produce gastrointestinal symptoms, diarrhea, severe abdominal pain, and ileus. Extensive ulcerative colitis or renal damage may be seen.

Phillips, R.; Karnofsky, D. A.; Hamilton, L. D., and Nickson, J. J.: Roentgen therapy of hepatic metastases. Am. J. Roentgenol. 71:826-833; disc. 833-834, May, 1954.

Radioactive Gold Seeds

Radioactive gold (Au^{198}) seeds as a source of gamma rays have been developed during the past three years and can be used in many situations in which one might prefer not to use the longer acting radioactive cobalt. Au^{198} seeds are being used as permanent implants as a substitute for radon seeds. The seeds may be made with relative ease by placing radioactive gold wire within thin-walled nonradioactive gold tubing and cutting to the particular length according to the intensity desired. The gold tubing filters out virtually all beta particles but allows more than 90 per cent of the gamma rays of the Au^{198} to pass through, its energy requiring less lead shielding than the gamma rays of radon. The Au^{198} seeds may be implanted in malignant tissue with the same type of seed applicators that are used for radon seeds, or they may be loaded into

nylon tubing, which can be threaded through the malignant tissue. The seed pattern is easily readjusted by pulling the tubing into correct position if the roentgenogram shows faulty alignment. No untoward or unusual reactions have been noted in the cases in which Au^{198} has been used. The clinical regression of tumor tissue has been comparable to that noted with other good methods of irradiation.

James, A. G.; Henschke, U. K., and Myers, W. G.: The clinical use of radioactive gold (Au^{198}) seeds. Cancer 6:1034-1039, Sept., 1953.

Treatment of Thyroid Cancers with I^{131}

Uptake of radioactive iodine (I^{131}) in the primary or metastatic lesions of forty-seven patients with thyroid carcinoma was studied to determine the criteria for I^{131} therapy. Of the forty-seven patients, thirteen had papillary carcinoma, seventeen had adenocarcinoma with varying amounts of colloid formation, and seventeen had carcinoma of the undifferentiated type. None of the patients with undifferentiated or papillary types of carcinoma showed any appreciable uptake of I^{131} in the primary or metastatic lesions. Eight of seventeen patients with adenocarcinoma with colloid formation had metastases, and three of these showed sufficient uptake for I^{131} therapy to cause diminution in size of the lesions. In only these three patients who were benefited by I^{131} therapy was the necessary indication present, that of functioning metastases. When in only three out of forty-seven, or 7 per cent, the lesions are amenable to radioactive iodine therapy, even though dramatic, it is obvious that early and adequate surgery is still the best weapon against this form of carcinoma.

Meckstroth, C. V., and Curtis, G. M.: Criteria for therapy of malignant thyroid lesions with I^{131}. A. M. A. Arch. Surg. 67: 187-193, Aug., 1953.

Detection of Hepatic Metastases

The term "hepatic radioactivity survey" describes the technique and preliminary results of the use of radioactive isotopes for the diagnosis and localization of hepatic neoplasms. Hepatic radioactivity surveys have been performed on a total of 283 patients, 187 of whom had proved primary neoplasms. Hepatic metastases were excluded by inspection and palpation after laparotomy, microscopic examination of biopsy material, and careful postoperative evaluation. Of the preoperative surveys, 181 were entirely negative (96 per cent diagnostic accuracy). Of fifty-three patients with proved hepatic metastases, the condition was diagnosed in forty-nine before surgery through the use of radioiodinated albumin, an accuracy of 93 per cent. Liver-function tests were only 43 per cent accurate. The condition could be diagnosed preoperatively by routine methods of investigation in only eleven out of the fifty-three. The factors that seem to influence the interpretation of the survey are: (1) presence of intraperitoneal fluid collection, (2) inflammatory processes in the liver, and (3) intra-abdominal inflammatory lesions, such as active peptic ulcer. When such lesions are present, false-positive results may be obtained.

Yuhl, E. T., and Stirrett, L. A.: Clinical evaluation of the hepatic radioactivity survey. Ann. Surg. 138: 857-862, Dec., 1953.

Irradiation Therapy in Hodgkin's Disease

In about 75 per cent of patients, Hodgkin's disease begins in the peripheral lymph nodes, and the superficial nodes are almost always eventually involved. The mediastinal and abdominal nodes, the lungs, and the spleen are the most frequent internal sites of involvement. Enlargement of the lymph nodes may be the only symptom, or weakness, fever, anorexia, nausea and vomiting, weight loss, or pruritus may also occur. Localized pain is usually noted before roentgenological evidence of bone lesions. Bone-marrow studies sometimes reveal multiple granulomas. Survival figures of persons with Hodgkin's disease correlate more closely with the clinical stage of disease than with the histopathological condition or any other factor. Intensive irradiation is used

alone or immediately after surgical excision. Two thousand tissue roentgens are delivered to the tumor within fourteen days. However, the dosage is individualized; large masses may require heavier amounts. To assure adequate dosage tolerance in diseased regions, prophylactic irradiation to possible future disease sites is not given.

Nice, C. M., and Stenstrom, K. W.: Irradiation therapy in Hodgkin's disease. Radiology 62:641-652; disc. 652-653, May, 1954.

Cervical Cancer—Radium Treatment

A plastic modification of the vaginal units used in the Manchester system of radium treatment of cancer of the uterine cervix is described. The authors have devised vaginal units made of plastic and have added certain improvements, while maintaining the size and therefore the physics of the Manchester system. Technical advantages of the plastic units include holes for inserters, which have been drilled and threaded, holes drilled at the top through which linen thread has been passed to secure the radium tightly and to facilitate its removal, and the fact that units can be interlocked after insertion to prevent slippage.

Hankins, F. D., and Hockin, J. G.: Radium treatment of cancer of the uterine cervix by the Manchester system; use of plastic vaginal applicators Am. J. Roentgenol. 68:272-274, Aug., 1952.

Immediate Hysterectomy Following Irradiation

The salvage rate with carcinoma of the uterine fundus may be increased if hysterectomy is done within twenty-four to thirty-six hours after preliminary irradiation. Delay of six to nine weeks in the removal of a cancerous organ does not seem advisable when hours or minutes may be important. Operation is usually not done immediately because of the technical difficulty encountered in a field undergoing irradiation reaction. It is felt that if the uterus is removed within a day or two after completion of preliminary irradiation with radium, radiation effects do not present a surgical problem. When the irradiation reaction reaches a peak in the remaining operative field, wound healing is well under way. This belief is confirmed by the ease of the surgical procedure and absence of postoperative complications in twenty cases in which hysterectomy was done promptly after irradiation. With this method of immediate hysterectomy, postoperative morbidity is reduced. Moreover, postoperative irradiation may be instituted sooner than would be possible if surgery was delayed.

Addington, E. A., and Betts, R. A.: Immediate hysterectomy following irradiation for carcinoma of the uterine fundus; a preliminary report. Am. J. Roentgenol. 69:442-444, March, 1953.

Uterine Cancer—Radioactive Cobalt Treatment

When used in radiation therapy, radioactive cobalt has several advantages over radium. It is less expensive and it is easy to handle. The beta particles have low energy and hence adequate filtration is furnished by elements of low atomic number. The authors use 0.5 mm. nickel. Aluminum, rubber, and plastics are also suitable. Co^{60} has a relatively short half life of 5.3 years as compared with radium 1590 years. In treating patients, the packing method with multiple small foci of radioactive material in the uterine cavity and the cervix is used. Cobalt will play an increasingly important part in the treatment of uterine cancer.

Johanson, C. E.; Östling, G., and Gåsström, R. V.: Treatment of uterine cancer with radioactive cobalt. (Co^{60}). Acta radiol. 36: 324-328, Oct., 1951.

Lung Cancer and Smoking

There appears to be general agreement that the exposure of living tissues to long-life radioactive isotopes may initiate the onset of a carcinoma. If an ordinary M6 tube is filled with cigarette or cigar ash, a reading varying from 70 to 170 counts per minute depending on the particular type of cigarette or cigar tested is recorded against a normal background of 12. The radioactive isotope in question is presumably the long-life radioactive isotope of potassium, K^{40}, from which beta

emanation is very active. These readings represent only a minute dose particularly as it is only cigarette or cigar smoke that is of significance. Radioactive particles are known to be actually deposited in the bronchial tree and, since there is very slow absorption, these tissues must be continually subjected to bombardment by active beta particles, which is confirmation of the statistical evidence linking inhalation of cigarette smoke with carcinoma of the lung.

Mulvany, D. K.: Lung cancer and smoking. [Correspondence.] Lancet 2:205-206, July 25, 1953.

Radiation Distribution in Cervical Carcinoma

The authors believe that present-day reports of radiation therapy of cervical cancer should include accurate correlation between details of therapy and final outcome in terms of both survival rates and normal tissue alterations. At the University of Pennsylvania, from 1940 to 1946, 258 patients were treated for cervical cancer, with a 45 per cent survival rate. By the use of orthographic pelvimetry as described by Hodges and Nichols, in which the geometric relation of the radium sources to the pelvic viscera and parametrium is depicted, it is possible to calculate radium tissue dosage. This is important, since in the past improperly constructed or improperly placed radium applicators could nullify the gains of previous roentgen-ray radiation. Proper dosage consideration includes not only points A and B of Tod, but also the tumor itself and the zones of the ureters, the bladder, and the lower bowel. It is thereby hoped that in the future it will be easier to assess more accurately the results of irradiation both as to survival rates and postirradiation complications.

Lewis, G. C., Jr.; Chamberlain, R. H.; Hale, J., and Payne, F. L.: Radiation distribution in the treatment of cervical carcinoma. Obst. & Gynec. 1:378-386, April, 1953.

Radioactive Cobalt in Cervical Carcinoma

Vaginal smears were obtained at frequent intervals during the treatment of sixty-seven patients with cervical carcinoma with Co^{60}, and up to one year following treatment. Three types of changes were noted cytologically: (1) Those observed in normal epithelial cells, (2) those observed in malignant cells, and (3) those observed as the result of a constitutional reaction of the patient. The cytological response to radioactive cobalt was contrasted with that observed after roentgen treatment and radium therapy. The clinical course of carcinoma of the cervix following treatment with Co^{60} as compared with the cytological response disclosed interesting points of correlation which seem to have some definite prognostic value.

Haam, E. von; Hendricks, C. H., and Morton, T. L.: Cytological studies on patients with carcinoma of the cervix treated with Co^{60}. [Abstr.] Cancer Research 12:303-304, April, 1952.

Chain Reaction

Could a proper detonator be found, it was just conceivable that a wave of atomic disintegration might be started through matter, which would indeed make this old world vanish in smoke.—Whetham to Rutherford, July 26, 1904.

Dr. George E. Pfahler

*An Appreciation**

Fifty-five of Dr. Pfahler's eighty years have been devoted to the science of radiology. An account of his activities and contributions in this field constitutes a veritable history of radiology in America. He is held in respect and affectionate regard by his colleagues throughout the world as dean of American radiologists. He belongs to the group of pioneers in radiology. Only three or four years after the publication of Roentgen's discovery, he began his roentgen-ray work in 1899 at the Philadelphia General Hospital where he was Assistant Chief Resident Physician. The Board of Managers of the hospital decided to buy a roentgen-ray machine and asked him to take charge of it. He had desired to become a clinician and was so intensely interested in internal medicine that he at first doubted the propriety of getting into a thing like radiological practice, which he thought had been already pretty much worked over, for the bones had been studied and foreign bodies had been demonstrated. He never gave up this idea of being a clinician and all his life he has so integrated his radiological practice into general medicine and surgery that he exemplifies the highest type of clinical radiologist.

Dr. Pfahler graduated from the Medico-Chirurgical College, Philadelphia, in 1898. He was intern at the Philadelphia General Hospital in 1898 and 1899; assistant chief resident physician from 1899 to 1902; Clinical Professor of Roentgenology in the Medico-Chirurgical College, 1909 to 1912; Professor from 1912 to 1916; Professor, now Emeritus, of Radiology, Graduate School of Medicine, University of Pennsylvania from 1916 on.

He began treatment of his first case of skin cancer in February, 1901, and reported four cases in September before the American Roentgen Ray Society. This report was published in *Therapeutic Gazette*, March, 1902, and in *Electrobiologie*. One of these cases is shown in Fig. 1. Just forty years later Dr. Pfahler reviewed 1580 cases of skin cancer with a cure rate of 98.7 per cent.

His first case of cancer of the lip was successfully treated beginning in April, 1903 (Fig. 2). Thirty-six years later he reported a large series of cases of cancer of the lip, 99 per cent of which had yielded to radiotherapy.

Already in 1896, as Dr. Pfahler later declared, roentgen rays were being produced in every laboratory of physics where high tension currents were being passed through Crookes tubes, and some of the penetrating effects of the roentgen rays were recognized even before Roentgen's discovery but were not sufficiently investigated. Dr. Pfahler himself recalls seeing the characteristic greenish light of a Crookes tube excited by a static machine in a demonstration of matter or gas in "radiant state" by Professor L. G. Cope in a lecture on physics in 1893 at Teachers College in Bloomsburg, Pa. This was

*By Dr. James T. Case, Santa Barbara, California, Past President of the American College of Radiology and President of the Inter-American College of Radiology, who was the first to use 200,000 volts in radiotherapy.

FIGURE 1. Case IV. A, White female, M.R., age 70, had a warty growth on the right side of nose for two years, which at times was very painful. Section removed on August 24, 1901, was reported as cancer by Dr. Joseph McFarland (Pathologist); referred by Dr. E. S. Gans (Dermatologist). The growth was 2.5 cm. Roentgen-ray treatment was begun immediately. B, Well more than five years.

his first but unrecognized experience with roentgen rays.

The equipment that he began using in 1899 was considered "a very powerful coil," which permitted him to make a "picture" of the hip or head in as short a time as eight minutes. He was currently interested in the diagnosis of brain tumors and he made two exposures of his assistant's head to get some standards of normal. The result was complete alopecia of the left side of the head but entirely satisfactory restoration of the hair in three months. Such experiences gave some idea of dosage values. Together with Dr. Charles K. Mills he made the roentgenographic diagnosis of the second case of brain tumor to be recognized by this new method.

There were no milliampere meters and no volt meters at that time, the voltage being estimated by the length of the point-to-plate parallel spark gap. The quality of the rays was judged by the appearance of the hand held in front of the fluoroscope, a test that led to the loss of fingers, hands, and even the lives of many pioneer workers.

In 1899 at the General Hospital in Philadelphia Dr. Pfahler set up a 6 by 6 foot grounded aluminum screen, 2 mm. in thickness, between the tube and the patient and himself, not with the idea of protection from the roentgen rays but to carry away any electrical currents; and he attributes his escape from the fate of the other pioneers to this screen. A few months later he replaced this screen with a smaller one attached to the tube holder and no longer grounded.

In 1904 Perthes made the first depth-dose measurements, which subsequently resulted in the use of filters in continental Europe and led to a more thorough investigation of the absorption rate in various media. Dr. Pfahler's interest in filtration was inspired by the report of the physicist Walther in 1905. He finally settled on wet leather as most nearly approximating the skin and found that with sole-leather filters a dose that would ordinarily cause necrosis of the skin could be given without damage, thereby permitting an increased depth dose. Later the leather filter was abandoned, increasing thicknesses of aluminum being employed. Copper next came into use as voltage became higher, later replaced by the Thoraeus filter, consisting of tin, copper, and aluminum.

Dr. Pfahler became a member of the American Roentgen Ray Society in 1902 and is one of the three oldest living members. He was elected the tenth president of the Society in 1910, the sixth president of the American Radium Society in 1921, and the first president of the American College of Radiology in 1923. He received the certificate of D.M.R.E. from Cambridge University in 1926 and was made an Honorary Fellow of the Faculty of Radiologists of London (1950). He is an Honorary Member of many European societies, as well as of the Mexican Radiological Society. Ursinus College in 1942 conferred upon him the Honorary Degree of Doctor of Science, and named a beautiful new science building the "Pfahler Hall of Science" in his honor. The principal address during the exercises was given by Dr. William D. Coolidge, the great inventor to whom radiology is so much indebted. Dr. Pfahler has been the recipient of the Gold Medal of the Philadelphia County Medical Society (1930),

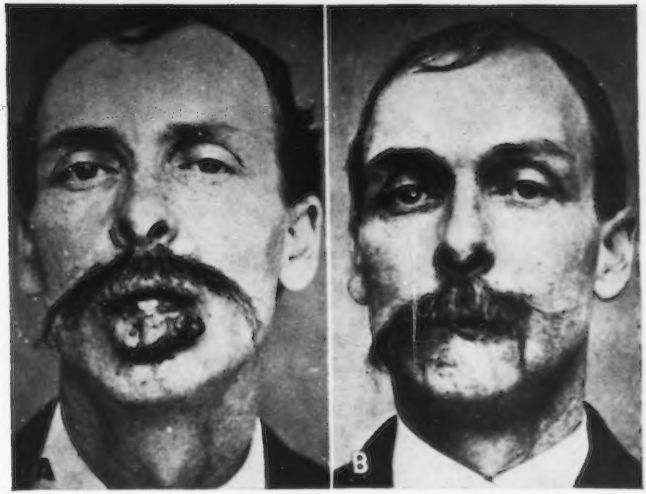


FIGURE 2. A, Male, age 41; cancer of the lip of eleven years' duration; began as a fever blister. He had previously been treated with caustics by a layman. Roentgen-ray treatment began May 25, 1903. B, The patient remained well thirty years and died of intercurrent disease.

of the American Radium Society (1935), of the American Roentgen Ray Society (1937), of the Radiological Society of North America (1951), of the American College of Radiology (1952), and, in 1954, he was nominated to receive the medal of the Centre Antoine Béclère, Paris.

Many mechanical devices for the improvement of roentgen-ray treatment have been published by this ingenious physician. Special techniques offered by him concerned, among others, the examination of the sphenoids, mastoids, and the bladder. He was a pioneer in the early fluoroscopy of the chest and abdomen, especially of the digestive tract, and to his early work many of us, including the writer, owe the inspiration that led to dedication to the specialty of radiology.

Dr. Pfahler is much to be admired for his devotion to radiotherapy. He is responsible for the development of Kingery's idea of a saturation method. This was done concomitantly with the heavy-dosage methods developed in Europe, especially at the Institute of Radium at Paris by Coutard and his pupils. Special attention was given to the treatment of cancer of the breast and of intraoral cancer. He wrote many papers on the use of a combination of surgery, electrothermic coagulation, and radiation.

George E. Pfahler is loved and admired for his culture, his scholarship, his integrity, his competence, his frankness, and his devotion to science. The memorable work of Schinz and his colleagues on roentgen-ray diagnosis was dedicated to five most notable pioneer radiologists—one each in France, Germany, Sweden, Austria, and, in the United States, George E. Pfahler. He is the sole survivor of the five.

Similarly Manuel and Francisco Arce, Madrid, dedicated their textbook on pediatric radiodiagnosis to five leading radiologists from France, Italy, Germany, and Switzerland, and to Dr. Pfahler.

Dr. Pfahler's published medical articles number about 350. His hobbies are photography, travel, and dogs.

Age does not deter this outstanding radiologist from continued full participation in his professional work. He is a living example and an inspiration to all of us.

Radiation Therapy in Cancer

Richard H. Chamberlain, M.D.

The use of radiation therapy in cancer includes its administration for essentially curative purposes and also for palliative relief that is often unattainable with any other agents now available. The wise employment of radiation therapy is blended of a considerable body of clinical experience and of exacting scientific disciplines in radiological physics and radiobiology.

The Physician Studies the Patient

Radiation therapy must be used with all of the clinical acumen at the command of the therapist. Due attention must be given to the patient's nutrition and general metabolism, his psychological state, and considerations of adjuvant drugs, and an ever watchful eye kept for the occurrence of complications or new developments.

Of particular importance is initial and continued watchfulness for evidences of metastasis that may necessitate major alterations in the plan of palliative radiation or the shift of a curative to a palliative objective. The manifestations of tumor spread through local extension, lymphatic spread, hematogenous spread, or through body cavities are varied, and their study worthy of considerable effort. Yet much is revealed to the simple exploring finger and the inquisitive eye, as well as to the modern refinements of roentgen-ray studies, marrow punctures, and blood chemical studies.

Methods of Radiation Therapy

New developments in electronic engineering and the by-products of atomic energy have greatly increased the scope of sources and methods for radiation therapy. A partial list of available methods is as follows:

1. External Beam
   - A. Low-intermediate-high voltage
   - B. Supervoltage
   - C. Gamma beam
   - D. Electron beam
   - E. Neutron beam
   - F. Proton beam
   - G. Cross-fire; Rotation
2. Interstitial Sources
   - A. Radium needles; Radon
   - B. Other isotopes—Co^{60}
3. Interstitial Colloidal Isotopes
   Au^{198}; Chromic Phosphate (P^{32})
4. Intracavitary
   - A. Roentgen rays
   - B. Radium; Radon; Other Isotopes—Co^{60}
   - C. Liquid Isotopes—Co^{60}
   - D. Colloidal Isotopes—Au^{198}
5. Parenteral Isotopes
   - A. P^{32}—Oral and intravenous
   - B. I^{131}—Oral and intravenous
   - C. Colloidal Au^{198}—intravenous
   - D. Others—Na^{24}

Much interest has been attracted to the use of apparatus that generates roentgen-ray beams at energies of one and two million volts up to twenty-two million volts and higher—commonly called supervoltage, but more properly called megavoltage apparatus. Some of these beams are essentially duplicated in apparatus employing very large amounts of radioactive isotopes and shielded so that their gamma beams may be used at a considerable distance and in quality ranges comparable to 400 to 2000 kv. roentgen-ray therapy. While no truly new, or radically different, effect is to be expected from this type of radiation, it is hoped that the ease of delivering larger doses to greater depths with less discomfort to the patient will justify their further development.

The use of electron, proton, and neutron beams is still in the experimental stage. Mechanical devices for improving the delivery of radiation to deeper parts by crossfiring and rotation-therapy techniques offer much promise.

In some instances, interstitial sources

From the Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

of radiation seem preferable because of the site and extent of the local tumor, and we have available greatly improved radium needles and radon seeds, as well as ingenious substitutes in Co^{60}, Au^{198} grains, radiotantalum wire, and other radioactive isotopes.

Interstitial radiation may also be delivered with colloidal radioactive isotopes of gold and phosphorus.

In the cavities of the body, the insertion of roentgen-ray beams and, in special instances, of the roentgen-ray tube target has been advantageously employed for special problems, such as cancer of the cervix. Radium, radon, or radioactive isotopes, such as Co^{60}, may also be used and have a major field of application in cervical cancer and in intraoral cancer. It is now possible to use liquid radioisotopes for the irradiation of cavities that may be filled, such as the bladder. Colloidal radioactive isotopes can be instilled into the peritoneal and pleural cavities, such as the use of Au^{198} for the control of malignant ascites and pleural effusions.

Radiation therapy of greater complexity, but of tantalizing promise, is found in the use of radioactive isotopes that depend on metabolic and physical localization when introduced parenterally. The most familiar applications of this principle are in the use of radioactive phosphorus, orally or intravenously, in the treatment of polycythemia vera and certain leukemias; and in the remarkable localization of radioactive iodine in certain metabolically active thyroid cancers.

The Radiological Physicist Co-operates

The computations of radiation dosage are now possible to a level of accuracy far beyond our clinical judgment. This has been made possible by development of radiological physics and is of great clinical importance because it avoids the summation of physical errors onto those resulting from the vagaries of malignant disease or the limits of medical knowledge. For beam radiations, full expressions of air, skin, and tissue dose can be derived either in selected planes or in three-dimensional contours. Dosage computations with radioactive isotopes are more difficult but are also probably of even greater importance because of the lesser experience with these agents. Radiological physics has also furnished us with a wealth of precision instruments for determining the distribution of radioactive materials, the control of beam-producing apparatus, and the analysis of the health and safety aspects of radiation hazards affecting patients, investigators, and innocent bystanders.

Radiobiology and Clinical Radiation Therapy

The newest field of investigation is in the actions of radiations on living tissues, both normal and malignant. Not only does this throw light on the efficacy of radiation therapy, but is also of importance in adding to our information concerning the characteristics of malignant disease itself. Some of the influences of cell metabolism and the interactions of hormones and chemotherapeutic agents on radiation sensitivity hold promise for future development. Though still in its infancy, this field of investigation is showing great promise in the explorations of dosage fractionation and the relative biological efficiency of different forms of radiation.

The Usefulness of Radiation Therapy

The treatment of cancer of the skin, lip, cervix, and fundus has been well established with radiation therapy as the definitive agent for curative management in a large proportion of cases. In many more instances, it is employed as the primary agent of choice in the hope that cure may be obtained, but with uncertainty as to whether palliation may be all that can be achieved. In frankly advanced cancer, palliative radiation therapy often achieves amazingly long management of a variety of tumors. A fragmentary list of advanced cancer situations in which it may be of major importance is as follows:

1. Bone: pain, fracture, disseminated disease.
2. Local: pain, ulceration, tumefaction, delay of spread, bleeding.
3. Lymph Nodes: ulceration, tumefaction, delay of spread, bleeding.
4. Pulmonary Metastasis: cough, bleeding, pain, venous obstruction.
5. Lymphomas and Leukemias: fever, malaise, local tumefaction, splenic enlargement.
6. Indirect Hormonal Effect: radiation to the ovaries.

Enthusiastic though we may be to obtain total and unequivocal cures for malignant disease, the prolongation of useful and enjoyable life is an equally noble aim for the physician.

We do not yet know how much more can be achieved with the further development of radiation therapy. There is little evidence that we can expect a great qualitative improvement in radiation effect, but much may be done in employing the most advantageous distribution of radiations, choosing the optimal radiation source for each problem, and employing the full cooperation of radiological physics and radiobiology. Combined with expert clinical judgment and humanitarianism, the physician can hope to make long strides in the best interests of the cancer patient. We need to use fully the agents and techniques that are already at hand. If we continue to develop and use new methods, we can expect still further improvement in the control of the growth of cancer and in the alleviation of the suffering that is caused by it.

The First Published Radioautograph

This reproduction is believed to be the first published radioautograph showing biological application of Becquerel's discovery of the radioactivity of uranium salts in 1896. It was published in the *Archives d'électricité médicale*, 12:363-372, 1904, from Paris. E. S. London, from Berlin, was responsible for this capital experiment. Two frogs were placed in separate hermetically sealed jars. The test frog was exposed to vapors from a small tube of radium connected to his chamber; the other was deprived of this experience. On the twelfth day, the first recorded self-photographed scientific martyr to radioactivity croaked his last, was placed on photographic film, and immortally interred in this silvery bier.

High Energy Radiations

Principles Underlying Newer Modalities of Treatment

John S. Laughlin, M.D., and James J. Nickson, M.D.

On a physical basis several advantages are predicted for the therapeutic use of roentgen rays with energies considerably greater than one million electron volts. These advantages all relate to the localization and definition of the radiation dose. They may be summarized as follows.

High Depth Dose

The greater penetration of the higher energy roentgen rays produces higher relative doses at great depths in the patient.

Low Skin Dose

The great range and forward direction of the associated secondary electrons produces a minimum radiation dose on the surface.

Main Dose beyond Surface

The great range of associated secondary electrons causes a definite maximum radiation dose to occur several centimeters below the surface. The actual depth depends on the energy of the roentgen rays employed.

No Side Scatter

The forward direction of both the secondary electrons and scattered roentgen rays results in a well-defined beam throughout the body with negligible sidewise scattering.

Low Bone Absorption

Although low energy roentgen rays are preferentially absorbed in bone, the higher energy roentgen rays are absorbed approximately equally by a unit mass of either tissue or bone. This decreases the probability of bone necrosis.

All of these physical factors are favorable to the use of high energy roentgen rays and should result in a much more favorable ratio of tumor damage relative to healthy-tissue damage than is possible with conventional low energy roentgen rays. These advantages are particularly pronounced with respect to the more deep-seated lesions.

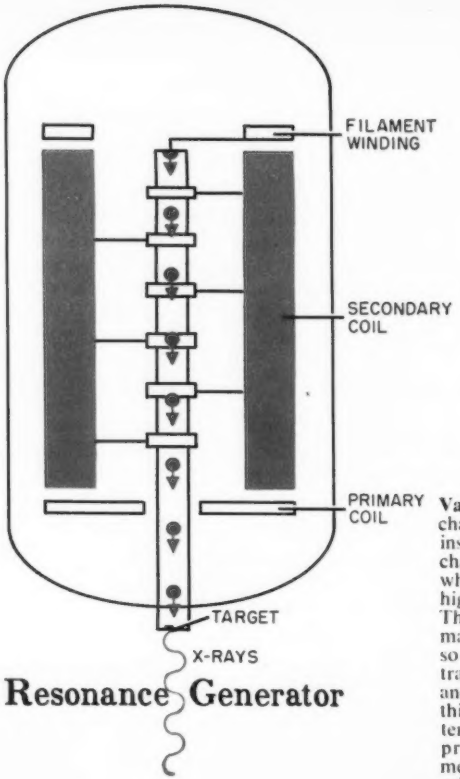
High energy electrons themselves also offer unique advantages for lesions located adjacent to the surface. This is a consequence of the definite range of electrons in tissue, which avoids radiation damage beyond the lesion.

Such machines as betatrons, linear accelerators, and synchrotrons accelerate electrons to high energies. The electrons can be used directly from these accelerators or can be directed against targets to produce high energy roentgen-ray beams.

Since accelerators have been applied to therapy only within the last few years, it is not yet possible to evaluate their clinical success definitely. The expected advantages of low skin dose and low total-body dose with consequent lessened radiation sickness have been definitely realized in practice. Whether or not these realized physical advantages of localization will result in a higher cure rate cannot yet be ascertained. In the case of some lesions there are encouraging indications in this direction. Experience with animals, bacteria, and humans so far indicates no fundamentally different biological actions in any qualitative sense. To date, the very real differences appear to be restricted to quantitative differences in distribution.

HIGH ENERGY RADIATIONS

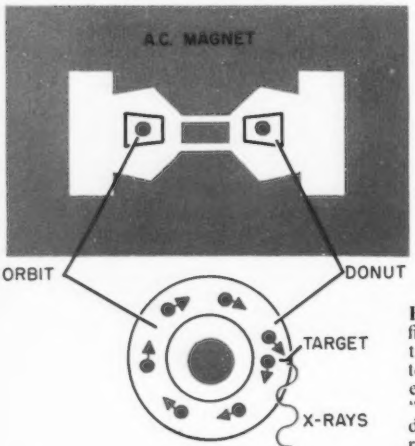
Principles Underlying Newer Modalities of Treatment



1-Mev Resonance Generator. This accelerator uses a resonant circuit to produce a potential difference across an evacuated tube. Connections from the secondary winding of the transformer distribute the difference of potential along the roentgen-ray tube. Electrons acquire energy as they traverse the tube and there strike a target and produce roentgen rays. The useful range is 1 to 2 Mev.

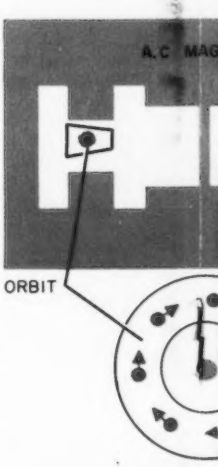
Resonance Generator

Van de Graaff. charge is sprayed insulated belt tha charge to an insul where it accumul high potential to The other end o maintained at gr so that electrons f traverse the lengt and can either p thin window and ternally or strike produce roentg medically useful million electron v

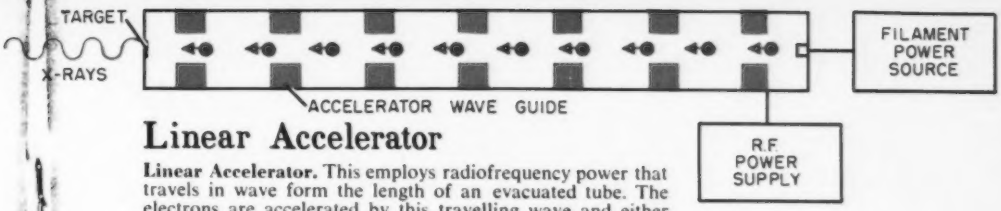


Betatron. An alternating magnetic field is employed to accelerate electrons travelling in a circular orbit to high energies. They travel in an evacuated tube, which is called a "donut" and may either be brought out directly or strike a target and produce roentgen rays. The useful range is 6 to 22 Mev.

Betatron



Synchr



Linear Accelerator

Linear Accelerator. This employs radiofrequency power that travels in wave form the length of an evacuated tube. The electrons are accelerated by this travelling wave and either pass through a thin window or strike a target and produce roentgen rays. The useful medical range is 4 to 50 Mev.

Graaff. An electric
is sprayed on a moving
d belt that conveys the
o an insulated electrode,
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tential to the electrode.
ner end of the tube is
ned at ground potential
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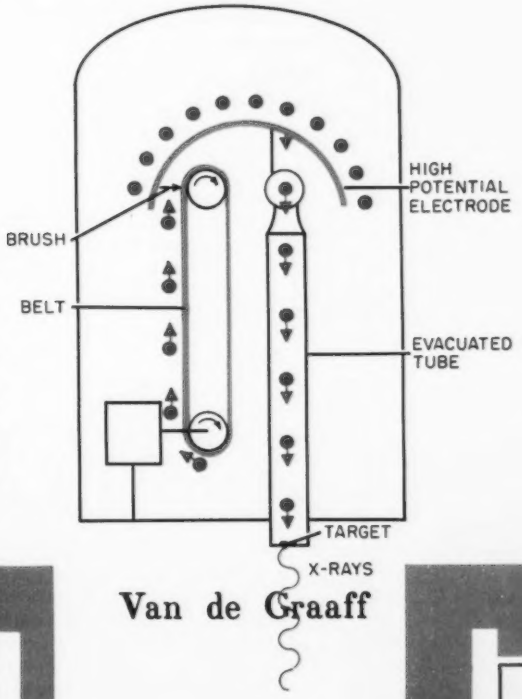
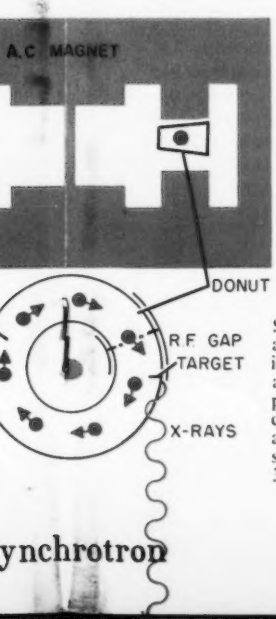
electron volts (Mev).

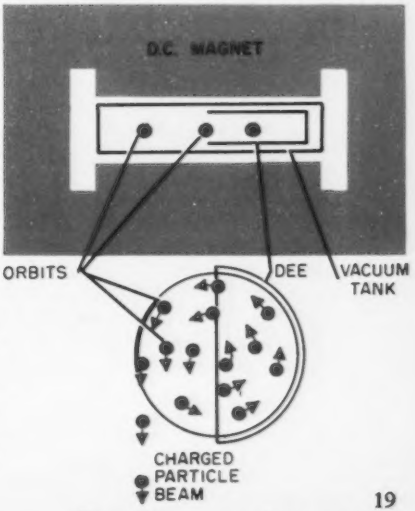


Van de Graaff

Synchrocyclotron. The synchrocyclotron accelerates charged particles (such as protons, deuterons, and alpha particles) that travel in increasingly larger circular paths in an evacuated chamber. The particles are accelerated by an electrostatic force at the edge of the electrode called a "dee." As the particles gain energy, their mass and rotational time also increases and therefore the frequency of the electrostatic field is also varied. The particles can be used to bombard an internal target or as an external beam.



Synchrotron. The electrons initially are accelerated by the magnetic field in a circular orbit. Subsequently they are accelerated by a radiofrequency potential. They are then brought out directly as an electron beam or strike a target to produce roentgen rays. The synchrotron is used medically in the 30- to 70-Mev range.



Synchro cyclotron

Concepts of Radical Irradiation Therapy

Milton Friedman, M.D.

Radical irradiation for advanced cancer, like radical surgery, accepts a degree of risk of damage to normal tissue in exchange for increased survival rates. Radiation damage may be tolerated as a permanent disability or may be repaired surgically. It can be minimized by special precision techniques based on a knowledge of the tolerance doses of normal tissues.

Before proceeding with the detailed discussion of the techniques, the premises on which they are based must be made clear.

Individualized Tumor Lethal Dose

Radical irradiation is reserved for advanced, radioresistant, or otherwise incurable cancers. It is distinct from orthodox concepts of dosage which "trend towards an optimum dosage which might be appreciably better than either a little more or a little less [irradiation] . . ."[5] In radical irradiation the statistical concept of an optimum dosage derived from retrospective analysis of series of cases is replaced by an individualized, aggressive attack on each tumor. The assignment of a specific dose as the tumor lethal dose for each type of tumor may result in adequate treatment of some of them. For example, the dose of 6500 r in three to five weeks is commonly used for tongue cancer, but the range of the tumor-lethal dose for tongue cancer is 4500 r to 10,000 r or more. Consequently, radioresistant lesions will be inadequately treated by the "optimum dose." The radioresistant lesion can be identified by the clinical picture, the slow rate of shrinkage during the first two weeks of roentgen-ray treatment, and by serial biopsies during the course of treatment. When interstitial radium is employed, the necessary selection of a predetermined dose prevents fitting the dose to the sensitivity of the tumor, and once again the radioresistant lesions may receive an inadequate dose.

From the Department of Radiology, New York University College of Medicine, and the Hospital for Joint Diseases, New York, New York.

Calculated Risk of Normal-Tissue Damage

Many tumors have a lethal dose that is larger than the amount of irradiation that normal tissues can comfortably tolerate. The tolerance doses of many normal structures are known.[1] A few examples are shown in Table 1.

These are ceiling doses below which no radiation injury will occur. Conservative irradiation, not exceeding these tolerance doses, foregoes the opportunity of eradicating a number of tumors. However, that these doses may be exceeded, with a calculated risk, is shown from an examination of the figures in Table 2.

Only 25 per cent of the stomachs receiving tissue doses ranging between 3500 and 4400 r are injured, and these injuries are minor, i. e., dyspepsia and spasm of the antrum owing to submucosal fibrosis. In the dosage range of 4500 to 5400 r, 50 per cent of the patients will be injured. These injuries tend to be more severe. Radiation mucosal ulcer will occur in 15 per cent of patients and perforation in 11 per cent. Nevertheless, in the presence of an inoperable cancer, the risks of radiation injury are warranted. Many injuries

TABLE 1

Tolerance Doses of Normal Tissues

Tissue	Dose, r	Given in, wk.
Stomach	3500	5–8
Transverse colon	4500	5–8
Central nervous system	5000	5–8
Small intestine	4300	5–8
Kidneys (part of each)	4000	5–8
Kidneys (whole of both)	2500	3–6

FIGURE 1. Case 1. Advanced carcinoma of the extrinsic larynx.

can be corrected by partial gastrectomy. In a desperate situation, where tissue doses ranging from 5500 to 6400 r are required, 37 per cent of the patients will escape radiation injury; and in this entire group, ulcer of the stomach with perforation will occur in only 18 per cent of patients.

The minimal tolerance dose for brain tissue is 5000 r, but tissue doses of 6000 to 10,000 r have been successfully given in order to arrest certain tumors.

To summarize, when the lethal dose of a tumor is much greater than the tolerance dose of the adjacent normal tissues, it is reasonable to accept the risk of irradiation damage to the latter. The percentage incidence of injury and the severity of the damage tend to be proportional to the tissue dose.

Supralethal Dose

When employing radical radiation therapy, one is always operating in the so-called supralethal dose range, i.e., greater than optimal range.

The author has not seen the type of supralethal-dose effect wherein a persistent or recurrent tumor is found within an area of severe radiation damage owing to a large tumor dose becoming less efficient. A more likely explanation of such a phenomenon is that the dose was infralethal to the tumor. In other words, a radioresistant tumor survived in spite of a tumor dosage large enough to damage normal tissues. Increased radioresistance occurs as a result of underirradiation rather than overirradiation.

The author agrees with Paterson's later concept of supralethal dosage, wherein, as the dosage rises beyond optimum, the percentage of injuries increases proportionately and may cancel out the advantage of the larger dosage. This is precisely the area in which the calculated risk of radical irradiation operates. This principle

TABLE 2

Incidence of Irradiation Injury of Stomach

Dose, r	No. of patients	Per cent injuries
2500–3400	15	20
3500–4400	32	25
4500–5400	61	50
5500–6400	22	63

FIGURE 2. Case 1. Moderate radiation sequelae six years after a skin dose of 7800 r in thirty-five days. The larynx is normal in appearance and function.

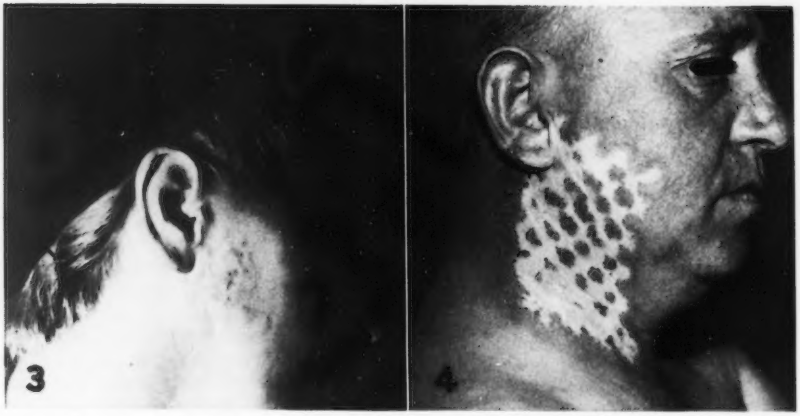


FIGURE 3. Case 2. Moderate radiation sequelae of skin, seven years after roentgen-ray therapy for recurrent adenocarcinoma of the parotid, Grade III. The skin dose was 7900 r in twenty-three days.

FIGURE 4. Case 3. Healed skin three months after irradiation through a perforated grid for extensive carcinoma of the tongue and tonsil with metastasis to nodes. The dose was 12,000 r (air) in five weeks. The lower pencil beam traversing the normal larynx produced chondronecrosis, requiring tracheostomy. The patient died four years later of generalized metastasis. The original disease never recurred.

obtains in a large series of cases when all patients are irradiated aggressively. Since radical radiation therapy is not employed in all cases, but only in the radioresistant or advanced cancers, incurable by conventional optimum dosage, the risk of radiation damage is small compared with certain death.

Techniques of Radical Radiation Therapy

Conventional Techniques with Very Large Doses. It is self-evident that the use of conventional techniques with very large doses must be included here as a form of radical radiation but it must be employed with care. Aggressive treatment of advanced carcinoma of the cervix with very large doses of radium and roentgen rays will cause severe and fatal injuries. For this type of lesion radical radiation therapy should be confined to roentgen-ray therapy only, employing precision localization with multiple portals or supervoltage roentgen-ray therapy. Another contraindication for large dose therapy is interstitial radium for intraoral lesions. The ensuing radionecrosis of bone produces severe morbidity, which seldom justifies the results. Advanced intraoral cancer can be more effectively treated and occasionally arrested with radical irradiation by combining intraoral cone with external irradiation, using 250 kv. roentgen rays to deliver tumor doses of 9000 to 11,000 r.[6]

"Single-Portal-Massive-Dose" Technique. This technique is employed for superficially situated tumors, not deeper than 4.5 cm. from the skin.[2] Using 250 kv. roentgen rays and a maximum field size of 8×10 cm., a total skin dose of 8000 r is delivered in five or six weeks to only one portal covering the primary tumor and the regional metastatic nodes. This dose is considerably in excess of the previously stated tolerance dose of the skin. It produces a third-degree skin erythema in only half the patients, which heals in one to three months. There was only one instance of radionecrosis, occurring when the dose was given over a period of three weeks instead of five to six weeks. The technique

FIGURE 5. Case 4. Radiation sequelae three years after irradiation through a grid of postoperative recurrent squamous-cell carcinoma of the middle ear, which had invaded the dura. The dose was 18,200 r (air) in forty-two days through an 8×8-cm. portal. There is no evidence of recurrence. Sequelae are much less than expected.

has been successful in many advanced cancers of the mouth and pharynx (Figs. 1, 2). Of twenty-four patients with advanced squamous-cell carcinoma of the mouth and pharynx, whose primary tumor was irradiated with this technique, fifteen were free of disease from six months to five years; six of these for two to five years. Two patients died of distant metastasis, the primary tumor having been controlled.

The technique was more effective against metastatic cervical nodes than against the primary tumor, because of the former's superficial location. Twenty-six patients with metastatic nodes were irradiated. Seventeen patients were free of disease from one to five years. Six others died of remote metastases, the cervical nodes having been controlled. The technique is well suited for inoperable metastatic cervical nodes.

Carcinoma of the parotid, primary or recurrent, can be efficiently irradiated with this technique, as the disease is usually less than 4 cm. deep from the skin (Fig. 3). Of seven patients with carcinoma of the parotid, five are free of disease from four to ten years. It is probable that with this technique irradiation may play a major role in the treatment of this disease.

Other miscellaneous tumors, superficially situated, may be irradiated with this technique. A bulky, recurrent chest-wall mass from carcinoma of the breast can be readily controlled, as far as specific mass is concerned. A rare patient will survive for many years.

Irradiation through a Grid. Irradiation was first aggressively used against human cancer by Marks, who produced primary disappearance of inoperable radioresistant lesions, such as metastatic squamous-cell carcinoma of inguinal nodes from carci-

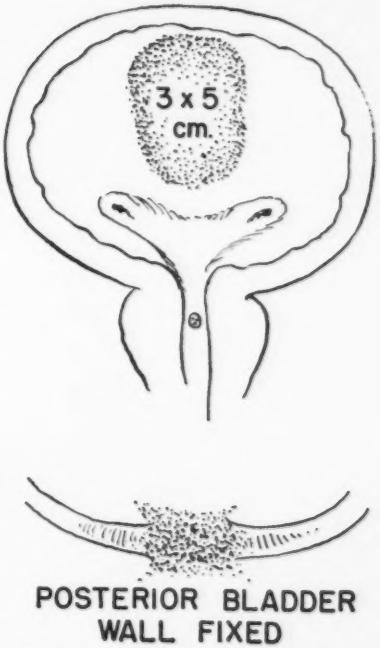


FIGURE 6. Case 5. Infiltrating carcinoma of the bladder, histological Grade IV, with extravesical extension and fixation of the bladder wall irradiated by the Walter Reed radium technique. The dose was 8500 gamma roentgens in seventeen days. The patient has a normal bladder five years later (see Fig. 7).

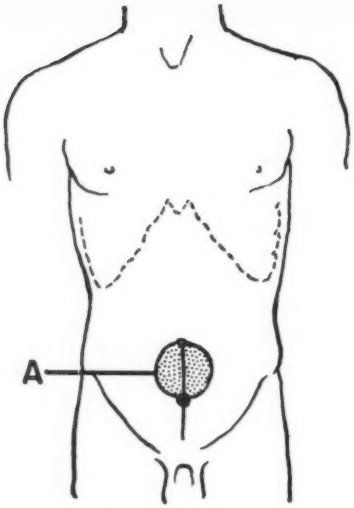


FIGURE 7. Case 5. Large tumor implant in the abdominal scar occurring five months after cystotomy and radium insertion in bladder. A, a 7-cm. spherical mass, deep in the abdominal wall; movable. Recurrent tumor was controlled with radical roentgen-ray and radium therapy; 7200 r was given in twenty-nine days and sixteen radon seeds for 3200 mc.-hr., equalling 5740 gamma roentgens. The patient is free of disease for five years.

noma of the penis. The grid permits delivery of a larger percentage depth dose, than through an open portal, though its impact on normal tissues is very destructive, especially when the irradiation is delivered through a single field (Fig. 4).

The grid is useful in salvaging extensive advanced squamous-cell carcinoma of the head and neck. In a series of thirty-nine such tumors, ten patients are free of disease from one to four years. Two of these, whose local lesion is controlled, have distant metastasis. Most of these patients were approaching the terminal phase of the disease and many had previous surgery or irradiation (Fig. 5). As proof, thirteen patients died within less than one year.

That the grid technique is a truly aggressive modality is evidenced by the fact that, in this series, chondronecrosis occurred in two patients whose larynx was not diseased, and necrosis of the mandible occurred in five patients. Each pencil beam of radiation is capable of producing severe damage as it traverses vulnerable tissue.

The optimum dose is 14,000 to 16,000 r (air) in five to seven weeks, provided the larynx is not irradiated. On occasion, one may venture a larger dose, and, if tolerated by the patient, a unique result may be achieved.

In conclusion, the grid technique is a somewhat crude, bludgeoning method of irradiating a patient but is capable of salvaging patients with widespread, advanced cancer of the upper respiratory tract, although the probability of radiation damage to the mandible and larynx is rather high.

Point-Source Intracavitary Radium for Bladder Cancer. The Walter Reed radium technique is used by a number of oncologists for cancer of the bladder.[3] In addition some use a point source of radioactive cobalt and some a solution of radioactive sodium. Most therapists treat only papillary carcinoma, as their results with infiltrating cancer are poor.

These failures are due in part to the thickness of the infiltrating tumor, so that the outer edge receives a relatively small dose as compared with the inner surface of the tumor. Since the alternative treatment of cystectomy is not very fruitful,

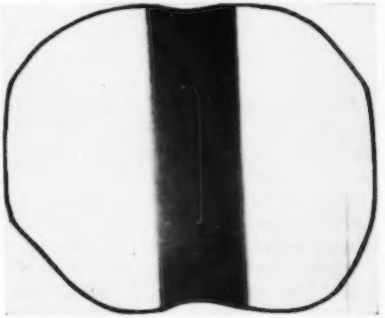


FIGURE 8. Distribution of radiation in the abdomen when two opposing portals (anterior and posterior) are employed with 2 million volt roentgen rays. All normal tissues from skin to skin are heavily irradiated with essentially the same dose.

the author has overdosed the surface of the bladder (8500 to 10,000 r in seventeen days) in order that all parts of the tumor receive a lethal dose. As a result, approximately 45 per cent of patients with infiltrating cancer have survived from three to seven years (Figs. 6, 7).

It was expected that all patients would suffer severe cystitis. However, about one third had only transient mild cystitis; one third suffered severely for about one year and were left with a contracted bladder, and one third varied between these limits. There were no fatal injuries.

This is a small price in terms of radiation damage to pay for these results.

Supervoltage Irradiation. Supervoltage irradiation (one and two million volts) readily permits of dosages much larger than the tolerance doses indicated in Table 2 being delivered to any part of the body. Successful irradiation of deep-seated radioresistant tumors (requiring lethal doses of 6000 to 9000 r) can be achieved. The use of two opposing cross-fire portals has led to severe injuries of the stomach, transverse colon, kidney, spinal cord, and small intestine because the vulnerable normal structures are heavily irradiated with approximately the same dose as the tumor (Fig. 8).

The two-portal technique with doses larger than 4000 r can only be used when these vulnerable structures are not in the pathway of the beam of radiation. There are specific indications for this type of radical radiation therapy. Fibrosarcoma

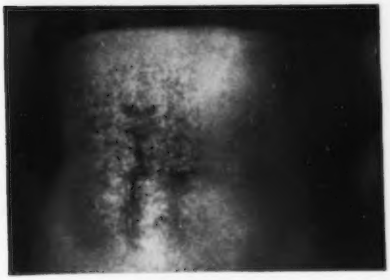


FIGURE 9. Case 6. Residual radiodermatitis in a patient with massive inoperable retroperitoneal fibrosarcoma, who is free of tumor ten years after irradiation.

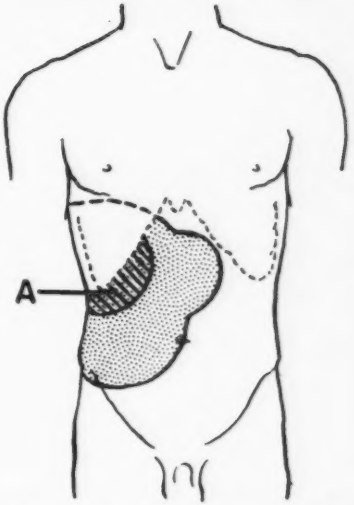


FIGURE 10. Case 7. Low-grade retroperitoneal fibrosarcoma fixed inside the peritoneal cavity and displacing the intestines and kidney; at A the superficial portion came up to the abdominal wall. After a tumor dose of 8356 r in sixty-three days, the tumor shrank more than 50 per cent in volume. The abdomen was reopened and tumor was mostly necrotic and easily removed. The patient is free of disease for five years.

of the extremities requiring tumor doses of 8000 to 10,000 r may be successfully irradiated on occasion. Massive inoperable retroperitoneal fibrosarcoma (Figs. 9, 10) that has displaced normal structures outside the beam of irradiation may be given large tumor doses of 6000 to 8000 r. There are five such patients who have survived from three to ten years. Case 6 (Fig. 9) had a massive retroperitoneal fibrosarcoma composed of vascular, friable tissue that could not be removed. She was irradiated through an anterior and posterior portal, 15×20 cm., the total skin dose being 5000 r per portal. The tumor dose was 6000 r in twenty-seven days. The intestines and stomach had been displaced and escaped injury. The right kidney, which lay within the beam, was destroyed. Three years after irradiation there appeared partial flaccid paralysis of both lower extremities owing

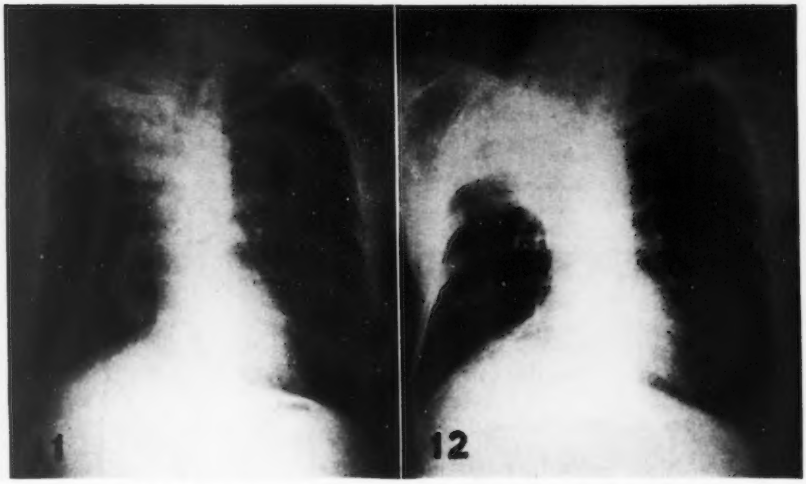


FIGURE 11. Case 8. Epidermoid carcinoma of the right upper lobe bronchus, before irradiation.

FIGURE 12. Case 8. The tumor was destroyed and the right upper lobe fibrosed six months after a tumor dose of 8816 r in forty days. The patient was followed for six years and then lost trace.

to spinal-cord injury. The patient is free of tumor for ten years. With multiple-portal techniques the latter injury might have been averted. Case 7 (Fig. 10) had a similar but more differentiated tumor that was found to be inoperable. Irradiation was carried out through multiple portals for a total tumor dose of 8356 r in sixty-three days. The tumor shrank, became mostly necrotic, and was then easily removed. There was no damage to any normal structure despite this enormous dose in the abdomen. The patient is free of disease for five years.

Lung cancer is seldom arrested with irradiation. The tumor doses required are almost twice the amount tolerated by the normal lung. Successful irradiation of the tumor is usually followed by death from radiation pneumonitis and fibrosis. The three successes achieved by the author occurred with upper-lobe lesions (Figs. 11, 12). This portion of the lung can be heavily irradiated through two crossfiring portals, destroying the lung, but not seriously impairing pulmonary efficiency. The upper lobe must be sacrificed to radiation destruction for the sake of tumor arrest.

Supervoltage Rotation Therapy. Supervoltage irradiation with rotation techniques constitutes the most important advance in radiation therapy in the past ten years (Fig. 13). It is particularly useful in radical radiation therapy, as it concen-

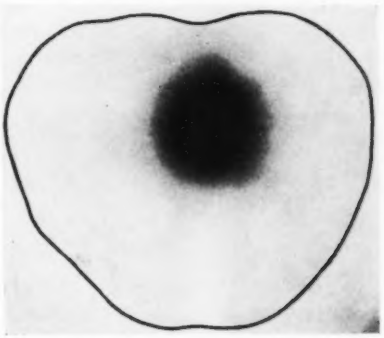


FIGURE 13. Supervoltage rotation therapy. Note the sharp localization of the 6-cm. diameter, heavily irradiated volume in the region of the body of the fourth lumbar vertebra, with minimal irradiation of the adjacent normal structures.

FIGURE 14. Case 9. Carcinoma of the nasopharynx, recurring three years after a tumor dose of 10,000 r in sixty-four days.

trates a large irradiation dose within a sharply defined volume and minimizes irradiation of adjacent normal tissues. It will probably replace many conventional techniques. Space limitations permit only a few representative examples but they encompass most of the principles.

FIGURE 15. Case 9. Chronic radiodermatitis, from a skin dose of 4800 r given five years ago, was not altered by supervoltage rotation therapy, which delivered to the nasopharynx an additional tumor dose of 7100 r in fifty days.

FIGURE 16. Case 10. Squamous-cell carcinoma of right antrum. Note the healthy skin three months after a tumor dose of 10,000 r in forty days from supervoltage rotation therapy.

Supervoltage rotation permits reirradiation of previously treated areas. Case 9 had in 1949 a locally extensive carcinoma of the nasopharynx that was irradiated with 250 kv. roentgen rays through five skin portals for a tumor dose of 10,000 r in sixty-four days. In 1952, symptoms recurred and a large defect was found in the base of the skull (Fig. 14). With supervoltage rotation, a tumor dose of 7100 r in fifty days was delivered. The disease was arrested. A recent photograph (Fig. 15) shows no aggravation of the radiodermatitis from the first course of irradiation. The patient has survived five years.

It had been difficult to irradiate carcinoma of the nasal accessory sinuses homogeneously with large doses. With supervoltage rotation therapy it is a simple matter to deliver tumor doses of 10,000 r to the antrum, ethmoid, or sphenoid region, without compromising adjacent normal tissues (Fig. 16).

Early cancer of the bladder can be treated by surgical or radium therapy. However, advanced cancer of the bladder

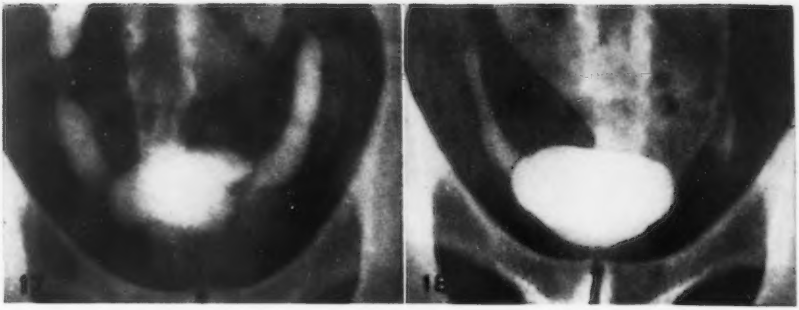


FIGURE 17. Case 11. Extensive infiltrating cancer of the lower portion of the bladder with bilateral hydronephrosis.

FIGURE 18. Case 11. Appearance of the bladder four months after a tumor dose of 9000 r in forty-one days. One year later the patient has a mild radiation cystitis; no tumor.

is not helped much by either method except in rare cases. Supervoltage rotation therapy can deliver large doses of radiation to the entire bladder and its environs. Figures 17 and 18 demonstrate a successful treatment. Thirty-eight patients with advanced bladder cancer have been irradiated with doses of 8500 to 10,000 r. Sixty per cent are free of disease from one to three years.

In advanced cancer of the cervix, thyroid, testis, and many miscellaneous tumors, supervoltage rotation therapy is an effective modality for radical radiation therapy. It can deliver larger doses to the tumor with fewer radiation injuries than any other technique and can arrest cancers that are otherwise incurable.

Summary

1. Radical irradiation entails the administration to the cancer of large doses of irradiation that may jeopardize adjacent normal tissues. This irradiation injury is acceptable within certain bounds as a calculated risk in order to arrest cancers that are otherwise incurable.

2. It is essential to know the tolerance doses of all normal tissues and the degree of injury produced by doses beyond tolerance. Two hundred and fifty kilovolt roentgen rays tend to injure the superficial structures. Supervoltage radiation tends to injure deeper structures.

3. Radical irradiation therapy is designed not as a routine technique but for special situations, such as radioresistant tumors whose lethal dose exceeds the tolerance dose of adjacent normal tissues, atypically resistant tumors that fail to respond to optimum dosage, and advanced, extensive cancer.

4. There are several techniques for radical irradiation therapy. Supervoltage rotation therapy is the ideal modality. It provides a large tumor dose with minimal irradiation of all normal tissues.

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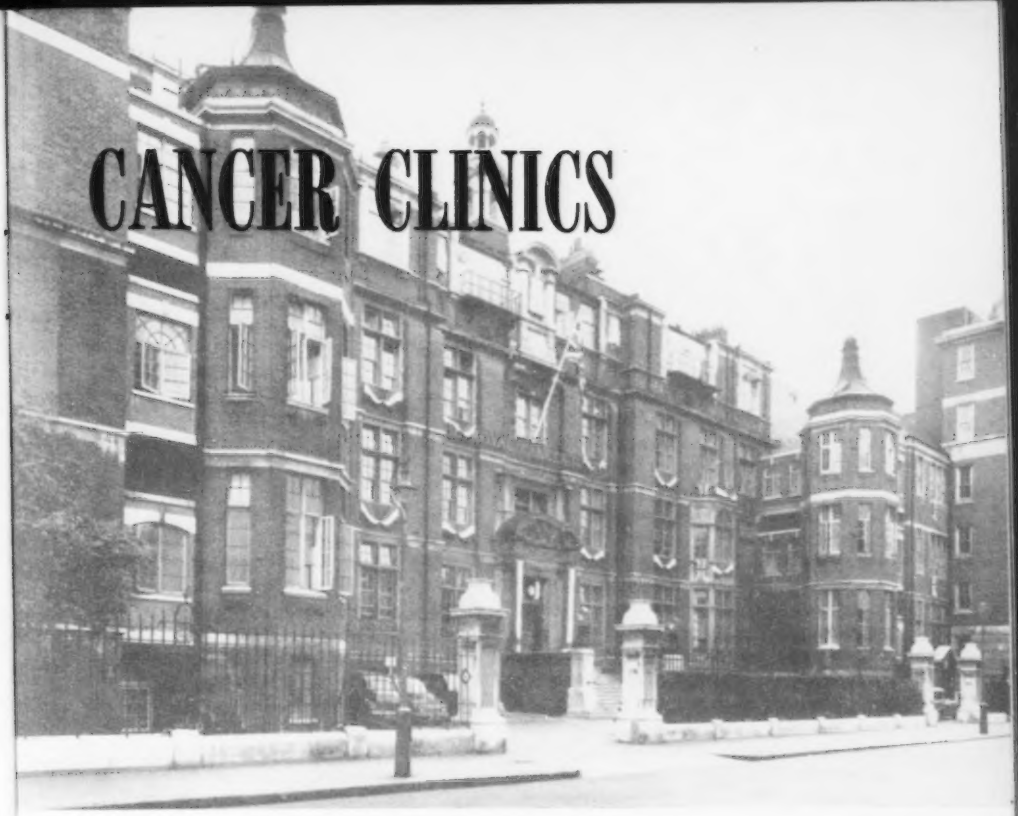
CANCER CLINICS



The Royal Cancer Hospital, London, S.W. 3., England

The Radiotherapy Department

Dr. M. Lederman, M.B., B.S., D.M.R.E., F.F.R., presiding

DR. LEDERMAN: In opening this discussion may I say first that radiotherapy is the term customarily employed to cover the medical uses of ionizing radiations whether the source of the radiation be a man-made machine, an artificially produced radioactive isotope, or a naturally occurring radioactive substance, such as radium.

For fifty years radium and roentgen-ray therapy have been the mainstay of the radiation treatment of malignant disease, but within recent years isotope therapy has become established and special types of apparatus, such as the betatron, synchrotron, and linear accelerator have been investigated or developed to a stage at which their clinical use is a practical possibility.

There is unfortunately no doubt that while the technical means of attacking cancer by radiation increase, the basic problems of cancer as a disease remain static and largely unsolved. A salutary and simple approach to the problem of radiations and cancer is therefore to try to evaluate established methods in the light of past experience and limit discussion to radium and roentgen-ray therapy and treatment by some of the commoner radioactive isotopes.

The vast majority of cancer sufferers throughout the world are treated by roent-

gen-ray or radium therapy; the part played by isotopes is a growing one but still relatively minor. While each form of treatment has its own particular indications, there are certain common purposes to which all radiation treatment can be put.

STUDENT: Is radiation employed in cancer solely as a curative agent?

DR. LEDERMAN: No. Radiation can be employed for purposes of cure, palliation, or as an adjunct to surgery in the form of pre- or postoperative treatment. The principles and technique of using radiotherapy for each of these purposes vary. The curative treatment of cancer by radiation is always a serious undertaking and reactions and complications and treatment risks have to be taken and accepted by the patient as part of the price to be paid for the chance of cure. By contrast, palliative treatment, which is unhappily the most common use, is reserved for cases wherein there is no reasonable prospect of cure. In these circumstances the aim is to prolong life in comfort by relieving distressing symptoms, such as pain, bleeding, or discharge, but without making the treatment a burden or otherwise adding to the patient's miseries.

RESIDENT: Under what circumstances is radiotherapy used in preference to, or in conjunction with, surgery?

DR. LEDERMAN: Help from the combination of surgery and radiotherapy is usually sought when there is some doubt concerning either operability or the completeness of an operation already performed. In the first case, it is hoped that a course of preoperative irradiation will bring a doubtfuly operable tumor into the bounds of operability, at the same time minimizing the risk of dissemination that may accompany the operative act by slowing down the growth rate of the tumor cells. In the second case, a postoperative course of radiation may be given in order to destroy any malignant cells conceivably remaining after the operation. It must be emphasized that postoperative radiation should be given only if there is reason to believe that malignant cells are present; and to be effective it must be given in full doses. There is no reason to believe that irradiation of normal tissues helps to forestall recurrence or prevent metastases, and the term "prophylactic radiation" still frequently used is therefore a misnomer, since radiotherapy cannot offer any counterpart to prophylaxis as understood by the immunologist. There is ample evidence to show that preoperative and postoperative radiation can be of definite value, particularly in the treatment of cancers of the breast, fundus uteri, upper jaw, and certain salivary-gland tumors.

VISITING PHYSICIAN: Is there any advantage of radium therapy over roentgen-ray therapy?

DR. LEDERMAN: In the past, much effort has been uselessly expended in contrasting radium and roentgen-ray therapy: essentially they are similar agents, each having developed its own particular sphere of usefulness while leaving a certain field wherein either can be used as an equally satisfactory alternative, the choice being frequently made on grounds of availability, technical simplicity, or economy.

Roentgen-ray therapy can be used in preference to radium therapy in the following circumstances: 1. Whenever the irradiation of large volumes of tissue is necessary, as is usually the case in dealing with radiosensitive tumors that disseminate widely or are systemic in nature, e.g., ovarian, testicular, and nasopharyngeal cancers, Hodgkin's disease, leukemias, and lymphosarcoma. 2. For the treatment of deeply seated and inaccessible cancers arising in the body cavities. It is physically and technically much easier to deliver adequate dosage at depth below the body surface by high-voltage roentgen rays than by any form of radium therapy. 3. For superficial cancers of the skin and lip. The results of roentgen-ray treatment for these lesions are just as good as those obtained by radium and it has the additional advantages of economy, speed, and simplicity. 4. For purposes of palliation. Roentgen-ray therapy imposes less strain on the patient, since individual roentgen-ray treatments are unusually short, the technique is simpler, and one tries to avoid allocating any part of a valuable store of

radium for palliative use when the same radium may be used for curative treatment.

Radium therapy should be used in preference to roentgen-ray therapy for the following conditions: (1) malignant tumors of moderate radiosensitivity that are limited in extent and are accessible or at the most situated at a limited depth below the body surface, for instance, carcinoma of the buccal cavity, larynx, pharynx, upper jaw, and cervix uteri and tumors of the anogenital region; (2) squamous-cell carcinoma deposits in lymph nodes of the cervical and inguinal regions.

This somewhat modest list of indications for radium treatment illustrates rather forcibly the modern trend in radiotherapy to restrict the use of radium to cases in which it can be shown to be either more successful or technically more advantageous than other available therapeutic agents.

STUDENT: Which of the several radioactive isotopes have been applied successfully in the treatment of cancer? What are the clinical indications for each of them?

DR. LEDERMAN: The advent of artificial radioactive isotopes in the field of cancer therapy has assisted the radiotherapist substantially from a purely technical point of view but has not as yet further increased the curability of cancer to any appreciable extent. While the number of radioactive isotopes available is legion, the actual number that have proved themselves of use clinically are few, the most important being phosphorus (P^{32}), iodine (I^{131}), gold (Au^{198}), tantalum (Ta^{182}), strontium (Sr^{90}), bromine (Br^{82}), sodium (Na^{24}), and cobalt (Co^{60}). The radiations emitted, the physical form in which the isotope can be made available, and the facility for protection provide each isotope with its own set of clinical indications. There are three main ways in which isotopes can be employed clinically:

1. *Selective Localization.* Radioactive phosphorus and iodine can both be used as a means of administering internal radiation. Phosphorus is selectively absorbed in the body by osseous and hemopoietic tissues and can be used as a method of treating polycythemia vera and chronic leukemia by beta radiation.

Radioactive iodine is readily taken up both by the normal thyroid gland and particularly in hyperthyroidism but unfortunately the cancerous thyroid gland does not appear to concentrate radioiodine. Nevertheless there is evidence to show that this isotope may be selectively taken up by the metastases if present, and this kind of selective uptake can be encouraged by thyroidectomy or thiouracil therapy.

There is no doubt that the selective localization of a given isotope in a specific tumor or tissue would provide an attractive and ideal method of treatment, but unfortunately this goal is as yet very far from being achieved.

2. *Replacement of Radium Sources.* Costly radium needles and tubes as used for implantation or surface application can satisfactorily be replaced by comparable radiocobalt sources; equally the modest quantities of radium (5 to 10 gm.) available for radium beam or teleradium therapy can also be similarly replaced. Radiocobalt has the further advantage that it is available in large quantities, as witness the large units containing 1000 or more curies now being brought into wide clinical use in the United States.

In the same way that gamma radiation similar to that obtained from a radium source can also be obtained from a cobalt source, so beta radiation can be obtained from a strontium or phosphorus source and these isotopes can therefore be substituted for radium whenever beta-ray therapy is required, e.g., particularly in ophthalmology.

3. *Isotope Solutions.* The fact that isotope solutions can now be obtained opens up a technical approach not previously available. Solutions of the isotopes bromine and sodium have been used for the treatment of bladder cancer, the solution being placed in a special bag and introduced into the bladder. The injection of colloidal radioactive gold solutions has also found wide use in the treatment of pleural and peritoneal effusions and more recently this isotope has also been used

for the direct infiltration of neoplastic tissues, in particular prostatic cancer.

There is no doubt that isotopes have helped considerably to extend the technique of radiation treatment, but it would be wrong at this stage to pretend they have materially altered the outlook for the cancer sufferer. The potentialities of this form of treatment, however, are considerable and must be fully explored.

INTERNE: Are cancers of certain anatomical sites more responsive to radiotherapy than are cancers of other sites?

DR. LEDERMAN: Yes. Certain forms of cancer can be cured by these methods, namely cancer of the mouth, skin, lip, cervix uteri, and larynx. For these sites radiotherapy competently administered is the method of choice and can effectively replace surgical treatment for the majority of cases. In other sites, such as the breast, fundus uteri, upper jaw, and paranasal sinuses, radiotherapy and surgery in combination offer most patients the best chance of success.

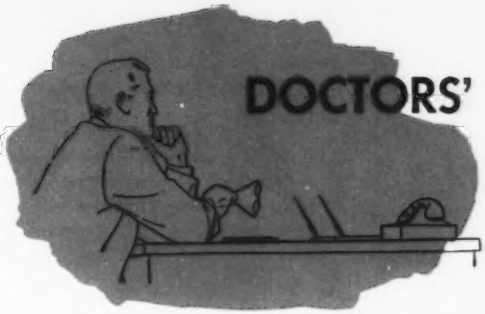
The inaccessible cancers of the body cavities, namely the intrathoracic, intracranial, and intra-abdominal tumors, are those wherein the surgeon should have priority, but unfortunately his scope is restricted by the late stage at which patients come to him. For this reason these cancers provide a suitable field for the newer, more powerful apparatus, such as the supervoltage roentgen-ray machines and telecobalt units.

Radiotherapy from a curative point of view has little to offer the patient suffering from a soft-tissue or bone sarcoma, although its value as a palliative or supplement to surgery is appreciable. Equally with the group of "lymphadenopathies," such as lymphosarcoma, reticulosarcoma, Hodgkin's disease, and leukemias, while radiotherapy does not cure in the usually accepted sense, it is the only method likely to help and its contribution toward prolongation of life and enabling a patient to continue his normal activities is frequently quite remarkable.

If one summarizes by surveying the field of achievement of radiotherapy, there is cause for both congratulations and humility.

Fluorescence of Cancer Tissue as Aid in Surgery

The fact that porphyrins accumulate in neoplastic, embryonic, and traumatized regenerating tissues of several species of animals and hematoporphyrin in lymph nodes and lymphatic tissues and tissues with a high mitotic index in general led Rassmussen-Taxdal, Ward, and Figge (Johns Hopkins Hosp. and U. Maryland Medical School) to administer hematoporphyrin to eleven patients scheduled for operation. The hematoporphyrin, in suitable doses, causes a red fluorescence in lymphatic and cancer tissues when viewed under ultraviolet light. In one case the cancer tissue could be seen under the skin of the breast and in another through the bowel wall. In others, the cancer fluoresced red when exposed at operation. It now appears possible to utilize the red fluorescence of hematoporphyrin and its tendency to concentrate in tumors to assist the surgeon to visualize and delineate neoplastic tissue during operations. The detection of small or obscure lymph nodes may also be facilitated by this method. The detailed report of this work appears in the January, 1955, issue of *Cancer*.



DOCTORS' DILEMMAS

Q *What is the recommended treatment for an area of leukoplakia on the buccal mucosa in a man of 46 who has been a heavy smoker for more than twenty years? I have urged that smoking be discontinued completely and have advised a complete dental check-up with whatever repairs are indicated.*

A The small areas of leukoplakia, not exceeding 1.5 cm., that are thickened and localized are best treated by surgical excision. This is not feasible in more widespread areas of involvement of the thin, filmy variety. All irritants, such as smoking, should be discouraged. Vitamin therapy affects localized lesions. Dental hygiene should be optimal.

Q *A patient with chronic cystic mastitis asks if she is likely to have cancer later. What answer should she be given and how should she be followed?*

A Fibroadenomatosis with cyst formation is a benign condition frequently confused with carcinoma. The patient should be watched at frequent fixed intervals and, if a dominant swelling develops, it should be removed and examined histologically. If there is no evidence of malignant change, no further treatment is necessary. If there is such evidence, immediate mastectomy is indicated. Chronic cystic mastitis in a woman 30 to 49 years of age multiplies her normal chance for cancer of the breast by 12.

Q *A 63-year-old woman had a left radical mastectomy two years ago. The pathological report was infiltrating duct carcinoma, Grade II, with no node metastases. She has been asymptomatic up to two months ago, at which time she noted the onset of low-back pain. Roentgenograms were taken and the radiologist reported evidence of bony changes involving L-1, -2, and -3. It could not be determined, however, whether the changes represented osteoarthritis or metastatic bone disease. The remainder of the skeletal survey was negative. What further can I do to determine the cause of the back pain and the nature of the roentgenographic findings?*

A It is, of course, generally recognized that women in this age group often develop osteoarthritis, which would account for this patient's symptoms. However, if this patient has metastatic bone disease and the changes are osteoblastic in character, certain chemical studies can be helpful: blood calcium, alkaline phosphatase, phosphorus. Elevation of alkaline phosphatase (once liver disease has been ruled out) would point rather definitely toward metastatic disease. So, too, would elevation of blood calcium in the event that the remainder of the skeletal survey shows no osteoporosis.

Q *A 28-year-old woman presents a discrete nodule about 2.5 cm. in diameter in the mid-line of ner neck anteriorly. She is otherwise symptom free. Should*

this nodule be removed for pathological examination? It has been present to her knowledge for about four months.

A There is a definite hazard involved in following the watch-and-wait policy in the management of thyroid nodules. Approximately 10 per cent of these tumors are cancer, and often the diagnosis is established only after careful microscopic examination. Cancer is more likely to be present in the single, solitary adenoma than in multiple thyroid adenomas.

Q *How much more frequently is cancer of the colon found in patients with a history of chronic ulcerative colitis than in the general population?*

A In a recent study of 1564 cases of chronic ulcerative colitis, it was revealed that cancer occurred approximately thirty times more frequently among these patients than in individuals of similar age groups in the general population. The marked increase in the incidence of cancer among these patients strongly underlines the need for careful, repeated follow-up examination of all persons with chronic ulcerative colitis and prompt investigation of any exacerbation of symptoms.

Q *Is cervical biopsy a recommended procedure for all patients with chronic cervicitis?*

A Early, unsuspected carcinoma in situ or early invasive carcinoma of the cervix may coexist with benign cervical disease. For this reason it is essential that biopsies be obtained from all cervical lesions. Whenever feasible, vaginal and cervical smears should be obtained and interpreted but this procedure is not a substitute for biopsy of the involved area. It is worth stressing the point that treatment should not be instituted until the biopsy report has been received from the pathologist in order that, should repeat biopsy be requested, additional tissue may be obtained from areas unaltered by treatment.

Q *What procedures are recommended to differentiate between benign and malignant gastric ulceration in a male patient 49 years old?*

A In the event that both roentgenological and cytological studies fail to differentiate between benign and malignant disease, a strict medical regimen of adequate diet, antispasmodics, antacids, and sedation may be prescribed. Repeat films of the gastrointestinal tract should be obtained at ten-day intervals, and, unless the area of ulceration has decreased by at least one half in size within three to four weeks, gastric resection should be performed without delay. In the event that surgery is not performed, further roentgenograms at more widely spaced intervals should be obtained.

Q *A 48-year-old Negro woman had a right radical mastectomy four years ago for cancer of the breast. Repeated follow-up examinations have shown no evidence of disease either locally or at some distant site. In the past six months she has begun to complain of intolerance to fatty foods, persistent eructations, and occasional right upper-quadrant pain. She has never had clay-colored stools or jaundice. Cholecystograms have shown a functioning gallbladder with multiple opaque stones measuring about 0.75 cm. in diameter on the average. I have requested surgical consultation and cholecystectomy has been advised. In view of the history of cancer, should this patient undergo such an operative procedure?*

A Previous surgery for cancer is no contraindication to additional surgery. The fact that the patient has already gone four years since her radical mastectomy indicates a favorable prognosis. It would seem wise to perform a cholecystectomy as recommended.

new developments in cancer

Cancer in Canada . . .

When less than 30 years of age, Indians and their white neighbors in Canada have the same incidence of cancer. When more than 30, the Indians apparently have less cancer. This is one of the findings by A. J. Phillips (Quebec) in a study of the endemiology of the disease in Canada. The study also shows that cancer of the skin is less frequent among the Indians and cervical carcinoma more frequent and earlier than among the whites. The incidence of cancer of other sites is about the same in both races.

Cancer in Vietnam . . .

The chewing of betel nut as a cause of buccal and pharyngeal cancers among the Vietnamese now appears debatable. B. Joyeux and N. L. Vien (Saigon) have found that an earlier indication of a reduction in the number of these tumors, accompanying a departure from the ancestral custom of chewing betel nut, may not be as significant as at first believed. It was thought that these cancers would be reduced as nonchewers matured into the "cancer-age bracket." On this theory, incidence graphs were projected in 1950 through 1954. Now in 1954, the Saigon scientists report, the projected lines are much lower than those supported by the actual incidence of these cancers. The investigators are convinced, however, that the use of betel nut has declined, particularly in women less than 40 years old.

Following Prostatic Cases . . .

Laboratory investigators of phosphatase and other blood changes in prostatic cancer, according to Stanley Way (Middlesbrough, Yorkshire), may be of help in: (1) confirming immediate diagnosis, (2) overcoming doubt in diagnosis, (3) controlling hormone dosage, and (4) warning of recurrences months before they are otherwise evident.

Soil Influences on Cancer . . .

Can soil types explain cancer types throughout the world? S. W. Tromp (Oegstgeest, Netherlands), reporting on studies by himself and J. C. Diehl, has classified prevailing kinds of cancer with sixty-four soil types found in the Netherlands. They found that the incidence of cancer decreased progressively from municipalities highest in peat soils to those with sea clay, sandy, cover sand, and river clay to loess soils in that order. Soil chemical compositions and drinking water, they believe, are responsible for the differences

in cancer incidence. The investigators feel that $CaCO_3$, Mg, Mn, and Na have a cancer-counteracting influence, while SiO_2 may have an activating effect. The lowest cancer death rates are in municipalities supplied with well water, highest in those using river water. On the basis of their own and others' studies, the authors have concluded that tuberculosis and other serious infectious diseases have an antagonistic effect in preventing later cancers.

Joint Disease . . .

The influence of hormones (elaborated by transplanted glands) on the development of degenerative joint disease in mice has been demonstrated by the Silerbergs and Opdyke (Washington U.). In the first month of life glands were removed from the male mice, or glands from closely related donors one to three months of age were transplanted subcutaneously. Transplants took readily. Additional pituitaries brought increased osteoarthritis—and brought it on one or two months earlier than usual. Castration alone decreased the incidence of disease, and the transplant of ovaries or adrenals or both further depressed the incidence and lengthened the latency of the disease in castrates.

Gland Transplants . . .

Gland transplants carried out for many years in hundreds of laboratory animals now are being used experimentally in humans; and preliminary results indicate that they may have value. Harry S. N. Greene, of Yale University, has transplanted pituitaries, thyroids, parathyroids, and adrenals to adults in trouble because of a deficiency or lack of these organs. The transplants are embryonic tissue—the donors, victims of miscarriages. Some of the transplants have been going for two years and they appear to be normally functional. The study began about ten years ago when Greene tested the autologous (within the same individual), homologous (within the species) and heterologous (between species) transplantability of tissues. He found that embryonic and cancer tissues were transplantable all three ways (with some limitations) and that normal and benign tumor tissues were not. One great dividing line in heterologous transplants seems to be the animal's ability to synthesize vitamin C—tissues are transplantable within species that can and within species that can't, but not between the two groups. If this rule holds good for higher orders of animal life, it may be possible to intertransplant between man and primates, for instance. So far, however, human experiments have been done only with human embryonic tissues.

Nerves and Growth . . .

Prof. Marcus Singer (Cornell Univ.) and others have found that nerves serve a purpose in growth almost as important as in transmission of impulses. Deprived of their nerve supply, tissues will not grow. This was demonstrated in, among other tissues, the regenerating limbs of salamanders and cats' whiskers. One of the nerve compounds necessary for growth (maybe the compound) is acetylcholine. When choline esterase (the enzyme which destroys acetylcholine), the dentists' novocaine, or the arrow poison, curare, was injected, growth ceased. Cancer, as usual, goes contrary to the rules. Cancers do not develop their own nerve supply, and consequently their growth is free of nerve control.

Cancer in Japan . . .

As compared with western population, Japanese have less cancer of the breast and lung and more cancer of the uterus, stomach, and liver, Katsuo Takeda (Sapporo) has reported. His findings are based upon an analysis of 4182 autopsies of malignant neoplasms. The study shows, however, that cancers of the breast and lung are increasing in Japan and those of the uterus, stomach, and liver are decreasing. Some of the increase of cancer in general is attributed to improved diagnosis and added longevity.

In an extensive study of the relatives of uterine-cancer patients, Murphy, (U. Pa.) found slight evidence of the condition "running in families." It occurred about twice as frequently among mothers and female relatives of patients as in the general population of women. A similar investigation of the families of breast-cancer patients showed no familial factors at all. The investigator concluded that "no evidence was found in either (breast or uterus) study to indicate that cancer in general occurred with any unusual frequency in cancer families."

Lombard (Mass. Dept. of Health) reported that, while the incidence of uterine cancer is increasing, deaths from it are on the downgrade. Five-year survivals noted in Massachusetts clinics rose from 27.8 per cent in the 1927 to 1936 period to 41.6 per cent for 1943 to 1947. He found uterine epidermoid carcinoma, both advanced and in situ, associated with marriage before the age of 20 years, divorce or separation, cessation of childbearing before age 25, unrepaired womb injuries, and syphilis.

Gagnon (Laval U., Quebec), reporting as gynecologist for seven orders of nuns, said cervical cancer is virtually impossible to find in convents. He did find, however, twelve cancers of the body of the uterus among 13,000 nuns examined over a period of twenty years -- an unusual pattern of pathology in the light of there being about four cancers of the corpus to one of the cervix in most North American clinics. In another study, covering twenty-five years, he noted 227 cancers of all organs, ten of the uterine corpus and no cancers of the cervix.

Gagnon's studies indicate that the absence of cervical cancers among French Canadian nuns is due to the absence of sexual activity. Cancer of the cervix constitutes about 16 per cent of all cancers among both French Canadian women in Quebec and the English women in Ontario. The incidence of breast cancer, on the other hand, was one third higher among nuns than among women generally. Cancer of the body of the uterus was only half in nuns what it is in the general population. Nuns, who are nonsmokers, had the same incidence of lung cancer as women in the general population; but Gagnon considered his figures eight cases, or 3.2 per cent of 222 cancers, too low to be of statistical significance.

Runge (Heidelberg, Germany) found similar correlations in German studies. Of 3000 cervical cancers treated over a forty-year period, only seven of the patients were

virgins. In one million healthy control women, 20 per cent had no children, as compared with but 7 per cent of the patients. The more children, the higher the frequency of cervical cancer. However, the latency of cervical cancer was only nineteen years for women with one child and an average of thirty-two years for women with eight or ten children. The older a woman was at time of her first delivery, the shorter the latency. He concluded that pregnancy delays the onset of cervical cancer; and he stated that cervical cancer can be prevented by clearing up lesions after delivery.

Runge reviewed gynecological records dating back forty years and found that cancer in situ (long considered nonmalignant) responded well to symptomatic local treatment. All but one of the sixteen cases followed twenty years remained healthy -- the lone exception being an invasive carcinoma discovered ten years after treatment. He opposes hysterectomy for noninvasive cancers in situ.

Freidell (Pondville, Mass.), reporting on 235 cases of preinvasive cervical carcinoma, said that leukoplakia of the cervix was found in 10 per cent of all the cases and some transitional changes in 50 per cent.

Higginson (South African Institute for Medical Research) reported that, while cervical cancer among South African native women is much more frequent than among North Americans (possibly related to the Africans' large number of pregnancies and various sexual customs), cancer of the body of the uterus is almost unknown.

Wynder (Memorial, New York) found that cervical cancer is from one fifth to one tenth as common among Jewish women in New York as among non-Jewish white women. The difference is even greater between non-Jewish women in New York and Jewish women in Israel. He cited other studies that showed that in India cervical cancer is about 45 per cent of all cancers among Hindu women, 29 per cent among Indian Christians, 18 per cent among Moslems, and 16 per cent among Parsis. The New York studies showed these factors associated with cervical cancer: early first coitus, early age of first marriage, multiple marriages, and lack of circumcision and hygiene among male partners. Negative variables included onset and flow of menses, method of delivery, irritative discharge, frequency of douching, gonorrhea, and sexual abstinence after menses and delivery.

(This report will be continued in the March Newsletter.)

COMING MEDICAL MEETINGS

Date 1955	Meeting	City	Place
Jan. 29-Feb. 3	American Academy of Orthopedic Surgeons	Los Angeles	
Feb. 4	American College of Radiology	Chicago	
Feb. 8-11	Mid-South Postgraduate Medical Assembly	Memphis, Tenn.	Peabody Hotel
March 28-31	American Academy of General Practice	Los Angeles	Shrine-Exposition Hall
April 7-9	American Association of Pathologists and Bacteriologists	Houston, Texas	
April 10-15	Federation of American Societies for Experimental Biology	San Francisco	Auditorium
April 12-14	American Association of Railway Surgeons	Chicago	Drake Hotel
April 15-16	[Eighth] Annual Cancer Symposium of the James Ewing Society	New York City	Memorial Center
April 15-17	Annual Meeting, American Association for Cancer Research	San Francisco	St. Francis Hotel
April 22-23	American Geriatrics Society	New York City	
April 23-30	Industrial Medical Association	Buffalo	Memorial Auditorium
April 24-26	American Association for Thoracic Surgery	Atlantic City	Chalfonte-Haddon Hall
April 24-29	Fifth Inter-American Congress of Radiology	Washington, D. C.	Shoreham Hotel
April 25-29	American College of Physicians	Philadelphia	Convention Hall
May 1	Federation for Clinical Research	Atlantic City	
May 9-13	Medical Society, State of New York	Buffalo	Hotel Statler
May 17-19	Massachusetts Medical Society	Boston	
May 22-25	American Association of Genito-Urinary Surgeons	Monterey, Calif.	
May 23-25	American Gynecological Society	Quebec, P. Q., Canada	
June 2-4	The Endocrine Society	Atlantic City	Chalfonte-Haddon Hall
June 2-5	American Medical Women's Association	Atlantic City	
June 6-10	American Medical Association	Atlantic City	

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